REMARKS

Claim 61 is the sole claim pending in the application. Applicants have amended claim 61 to recite that the nonpeptidyl agent which contacts the CD4+ cell is capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell. Support for the amendment to claim 61 is found, *inter alia*, in the specification at pps. 31-36 and particularly in Table 1 on page 32 and Table 2 on page 35. Accordingly, the amendment to claim 61 involves no issue new matter. Entry of this Amendment into the file of the present application is respectfully requested as the amendment to claim 61 is believed to place the claim in condition for allowance, or at a minimum to reduce the issues for an appeal.

The Claimed Invention

The invention as recited in (amended) claim 61 is directed to a method of inhibiting HIV-1 infection of a CD4+ cell. The method comprises contacting the CD4+ cell with a nonpeptidyl agent, said nonpeptidyl agent capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell, but not a CXCR4 receptor on the surface of such PM-1 cell, in an amount and under conditions such that fusion of HIV-1 or an HIV-1-infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner stated that claim 61 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the Examiner's rejection, applicants respectfully traverse for the reasons set forth below.

The Legal Standard For Enablement

35 U.S.C. §112, first paragraph, states that "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, . . ." (emphasis added). "Enablement . . . is determined as of the filing date of the patent application." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81 (Fed. Cir. 1986).

"Enablement is not precluded by the necessity for some experimentation such as *routine screening*. However, experimentation needed to practice the invention must not be undue experimentation. . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable

amount of guidance with respect to the direction in which experimentation should proceed. The term 'undue experimentation' does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. . . . Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the Board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (emphasis added, footnotes omitted).

"[I]t is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts . . ." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016 (Fed. Cir. 1991)

The Claimed Invention Is Enabled

The Examiner stated that the claim is broadly directed toward a method for inhibiting HIV-1 infection of CD4+

cells through the administration of a non-peptidyl inhibitory agent that is capable of binding to a chemokine coreceptor required for viral entry. The Examiner additionally stated that, as noted above, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The Examiner stated that the disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The Examiner stated that the disclosure fails to provide any guidance pertaining to the structural requirements of any given non-peptidyl inhibitor that is not a bicyclam or derivative thereof. The Examiner stated that the disclosure fails to teach which chemical structures are critical for binding to any given chemokine coreceptor and which structures are critical for the antiviral activity. The Examiner stated that the disclosure fails to identify any parent compounds, or derivatives thereof, that can reasonably be expected to function in the desired manner. The Examiner stated that the skilled artisan has thus been extended an undue invitation to further experimentation to try to identify putative antiviral agents and to determine their structure.

2) The Examiner stated that the disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating HIV-1 envelope/coreceptor/antiviral

binding interactions. The Examiner stated that in order to rationally design a putative therapeutic, the skilled artisan would need knowledge of those portions of CCR5 or CXCR4 that should be targets of any given antiviral. The Examiner stated that the specification is silent pertaining to this concern and fails to identify any critical regions of the chemokine coreceptors that should be the targets of antiviral development.

In response to the concerns set forth in items no. 1 and 2 above, applicants respectfully direct the Examiner's attention to ¶¶14-17 of the Declaration Under 37 C.F.R. §1.132 of Tatjana Dragic submitted as Exhibit B to applicants' Amendment filed April 8, 2002 in the present application (Dr. Dragic's "prior declaration"). In paragraph 14 of the subject declaration, Dr. Dragic states that, "[I]t is not necessary for one of ordinary skill in this art, searching for nonpeptidyl agents which will bind to a CCR5 chemokine receptor located on a CD4+ cell so as to inhibit fusion between HIV-1 or an HIV-1-infected cell and a CD4+ cell, to know in advance the structure of the agent." To support her statement, Dr. Dragic attached as Exhibit 3 to her prior declaration a copy of an Abstract by Olson et al. entitled, "Identification of CCR5 Coreceptor Inhibitors That Potently and Selectively Block HIV-1 Replication" (the "Olson et al. abstract"). Dr. Dragic was a co-author of the subject abstract, which was presented at the 9th Conference on Retroviruses and Opportunistic Infection held in Seattle, Washington from February 24-28, 2002.

As pointed out by Dr. Dragic in ¶15 of her prior declaration, the Olson et al. abstract provides data which demonstrates that using the Resonance Energy Transfer ("RET") method of screening as taught in the specification of the present application (see, for example, pp. 5-6 and 19-20), nonpeptidyl compounds were identified that are useful in the claimed invention **without** prior knowledge of the structure of these nonpeptidyl compounds and **without** the need for any undue experimentation, i.e., only routine screening methods, well known to those of ordinary skill in this art, were required. Dr. Dragic further stated in her prior declaration (¶15) that, as set forth in the Olson et al. abstract, following high throughput screening of a chemical compound library, a cell-based RET assay identified multiple compounds. These compounds, and analogs thereof, were then further characterized using secondary assays (see discussion below). Dr. Dragic thus concluded in ¶15 of her prior declaration that the Olson et al. abstract discloses that **without** advance knowledge of the structure of the compounds that specifically block CCR5-mediated, but not CXCR4-mediated HIV-1 cell-cell and virus-cell-fusion, compositions, including non-peptidyl compounds, were readily defined without the necessity for any undue experimentation.

In ¶16 of her prior declaration, Dr. Dragic noted that the "secondary assays" mentioned above are described in the Olson et al. abstract as employing a series of env-complemented luciferase reporter viruses, as well as

primary HIV-1 isolates. Dr. Dragic further stated that these assays are discussed in detail at, for example, pages 31-34 of the present application and that the results of the use of these assays are summarized at Table 1 on page 32 and Table 3 on page 37 of the specification. Dr. Dragic thus concluded in ¶16 of her prior declaration that this disclosure clearly established that luciferase assays, as in the Olson et al. abstract, were also well understood by one of ordinary skill in the art at least as of the filing date of the present application.

Based on the above, Dr. Dragic thus stated (in ¶17 of her prior declaration) that, in summary, even **without** prior knowledge of the structure of the compounds sought, but with knowledge of their desired use, one of ordinary skill at the time the invention was made would be readily able, relying upon the detailed teachings or guidance concerning the RET assay provided in the present application, to determine without any undue experimentation appropriate non-peptidyl agents useful in the claimed method, which claim is clearly commensurate in scope with the disclosure of the invention as taught in the specification of the application.

Dr. Dragic's prior declaration, for the reasons above, thus clearly and unambiguously establishes that it is not necessary to know the structure of the agent or of the molecular determinants modulating HIV-1 envelope/coreceptor/antiviral binding interactions, as postulated by the Examiner in points 1 and 2 on p. 2 of the

Office Action, in order to enable one of ordinary skill in this art to practice the claimed method of the invention. In order to overcome the evidentiary weight to which the statements in Dr. Dragic's declaration are entitled, the Examiner may not rely, as he has done here, simply on his unsupported opinion of what scope of disclosure is required to enable one of ordinary skill in this art to practice the invention. The Examiner must point to some tangible source, i.e., a patent, treatise, journal article or some other disclosure, to "disprove" the contentions set forth in the declaration and this he has not done.

The decision of the Federal Circuit in *In re Alton*, 76 F.3d 1168 (1996) deals, *inter alia*, with a situation which is analogous to the present circumstances. In *Alton*, the applicant had provided an evidentiary declaration of one skilled in the art under 37 C.F.R. §1.132 ("the Wall declaration") to support his contention that the specification of his application contained a sufficient written description of the claimed invention. The Examiner, and later the Board of Appeals, gave no weight to the declaration, characterizing it (at p. 1171) as being, "[A]n opinion affidavit on the ultimate legal question at issue", and thus provided no rebuttal to the points raised in the declaration.

The Federal Circuit, however, held that the Examiner had erred in summarily dismissing the declaration without an adequate explanation of why the declaration failed to rebut the *prima facie* case of inadequate description. It is

applicants' contention in the present case that reliance by the Examiner on his personal opinion, without "backing up" that opinion with the teaching of some tangible source (patent, etc.) amounts to a lack of an adequate explanation as to why Dr. Dragic's declaration failed to overcome the lack of enablement rejection raised with regard to the presently claimed invention. Applicants further contend that in the absence of such an adequate explanation, the statements of Dr. Dragic in her declaration are entitled to be accorded evidentiary weight.

Further to the above, in the specific context of declarations provided under 37 C.F.R. §1.132 to establish enablement, §2164.05 of the Manual of Patent Examining Procedure ("MPEP") states:

> The Examiner must . . . weigh all of the evidence before him . . ., including the specification and any new evidence supplied by the applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all of the evidence (emphasis in original).

Applicants submit that the Examiner of the present application has apparently relied on his own opinion of how matters stand in the art to counter the points raised in the Dragic declaration since he has not supplied any supporting written evidence to back up his statements. Applicants therefore respectfully contend that the Examiner

has thus not carried his burden of overcoming the evidence presented in Dr. Dragic's declaration.

Further to points 1 and 2 discussed above, the Examiner stated, with regard to the factual inquiries set forth in the *Wands*, *supra*, decision that:

3) The disclosure fails to provide any working embodiments that meet the claimed limitations. The Examiner stated that while it is noted that the disclosure described the identification of a putative antiviral agent (e.g., JM3100), nevertheless, this compound is a bicyclam agent and does not fall within the claimed limitations. The Examiner stated that there are no other examples involving non-peptidyl agents provided in the disclosure.

In response to item no. 3, applicants submit that the specification teaches that agents (peptidyl and nonpeptidyl) shown to inhibit fusion between an HIV-1_{JR-FL} envelope expressing cell and a $CCR5^+$ cell in vitro as determined using the Resonance Energy Transfer assay (RET) applicants, inhibits HIV-1 infection of $CD4^+$ cells in vivo. Applicants have exemplified peptidyl compounds (anti-CCR5 monoclonal antibody) inhibiting fusion between a HIV-1_{JR-FL} envelop expressing cell and $CCR5^+$ cells in vitro as determined using the RET assay (see page 12 and Figure 9 of the specification) and have provided herein evidence that peptidyl compounds inhibit HIV infection in vivo as demonstrated by a sustained reduction in viral load (¶16 Dragic Second declaration). The specification also teaches

that nonpeptidyl agents shown to be fusion inhibitors as determined by the RET assay in vitro have utility in inhibiting HIV-1 infection in vivo. Support of the validity and enablement of these teachings for nonpeptidyl agents is provided and expanded on in Dr. Dragic's Second Declaration Under 37 C.F.R. §1.132 detailed below.

The Examiner then went on to state in the Office Action that:

4) The claims are of excessive breadth and encompass any given putative antiviral agent without providing any meaningful structural limitations concerning that agent. The Examiner stated that the disclosure simply fails to support such breadth in the claim language.

The argument raised in point no. 4 by the Examiner is analogous to that set forth in points 1 and 2 above, i.e., that the structure of the antiviral agents and/or of the determinants must be known in order for the claimed method to be enabled. In response, applicants reiterate (and expressly incorporate herein by specific reference thereto) the arguments made above concerning the Examiner's points 1 and 2, i.e., that as evidenced by the statements in Dr. Dragic's declaration, it is <u>not</u> necessary for one of ordinary skill in this art to know in advance the structure of the agent in order to practice the method of the invention due to the disclosure contained in applicants' specification which readily teaches one <u>how</u> to obtain

nonpeptidyl agents which will operate in the claimed method without the need for any undue experimentation.

The Examiner's next stated that:

5) The prior art describes a number of concerns pertaining to the development of fusion inhibitors. The Examiner stated that first, it is well-known that the chemokine family includes a large number of proteins that share limited genetic relatedness (~ 20%)(Proudfoot et al., 1999: Proudfoot et al., 2000). The Examiner stated that thus, it appears unlikely that any given inhibitor will have a broad range of activity, particularly in the absence of the identification of any critical molecular determinants that are shared by all members of the family. The Examiner stated that second, even if a putative antiviral compounds was identified, there are a number of important immunological of therapeutic concerns that need to be considered (Berger et al., 1999). The Examiner stated that for instance, will the loss of normal chemokine receptor function of a specific coreceptor be tolerated and accepted in the host? The Examiner stated that will the impairment of CCR4 coreceptor usage accelerate disease progression by enhancing the selection for CXCR4 coreceptor usage? The Examiner stated that do multiple members of the coreceptor repertoire need to be blocked in order to achieve a therapeutic effect? The Examiner stated that the disclosure is silent pertaining to these concerns.

6) The Examiner additionally stated that the prior art (Öberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997) also provides a number of generic concerns pertaining to the development of any given putative antiviral compound to inhibit HIV-1 infection. The Examiner stated that it has been well-documented in the prior art that the development of suitable HIV-1 therapeutics has been a long and arduous process, often ending in failure to understand the molecular determinants modulating many viral protein and host cell factor interactions, the failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy, the failure of many compounds to have acceptable pharmacological profiles, despite initial favorable *in vitro* and *in vivo* activities, and the failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The Examiner stated that the difficulties associates with developing efficacious anti-HIV-1 agents are best summarized by Gait and Karn (1995) who state (see Conclusions, p. 37):

There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivities for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as

sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The art cited by the examiner, Oberg and Vrang, 1990 discuss screening systems as of 1990 for evaluation of drugs to treat HIV/AIDS. While the authors state that the relevance to different screening methods for predicting clinical efficacy "is at present uncertain... the predictive value of the screening systems is expected to improve". Oberg and Vrang do not disclose a RET assay for screening as described in Litwin et al and in the present invention and do not disclose viral fusion inhibitors.

Yarchoan and Broder, 1992 discuss general classes of agents as therapeutics against HIV including compounds that inhibit viral binding. While they may have stated their view that there is no correlation between in vitro assays and in vivo results, they have not closed the door to these compounds as potential therapeutics as stated on page 103, third paragraph:

> It is conceivable that such agents may eventually find clinical utility in preventing primary infection with HIV or in preventing perinatal transmission.

As in Oberg and Vrang, Yarchoan and Broder fail to disclose a RET assay for screening and fail to disclose HIV-1 fusion inhibitors.

Gait and Karn, 1995, as pointed out by the Examiner discusses problems associated with development of protease inhibitors as discussed above.

Flexner and Hendrix, 1997 discusses nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors as therapeutics against HIV. Flexner and Hendrix fail to disclose HIV-1 fusion inhibitors or methods of screening for HIV-1 fusion inhibitors.

Applicants submit that the references cited by the Examiner are not directed to HIV-1 fusion inhibitors for use in a method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with a nonpeptidyl agent in an amount and under conditions such that the fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited so as to thereby inhibit HIV-1 infection of the CD4+ cell. The references are totally silent as to nonpeptidyl HIV-1 fusion inhibitors. Moreover, the cited references fail to describe a screening assay for selecting nonpeptidyl agents capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell, but not to a CXCR4 receptor on the surface of such a PM-1 cell so as to inhibit fusion as may be determined using a RET assay. Thus, any discussion by the authors of the cited art as to difficulties in screening or in optimizing in vivo parameters is not germane to applicants' method of treatment using nonpeptidyl HIV-1 fusion inhibitor agents.

Applicants submit that the additional references cited by the examiner, Proudfoot 1999, Proudfoot 2000 and Berger 1999, dated after applicants priority date, supports rather than cast doubt on the enablement of applicants claimed invention. Both Proudfoot 1999 & 2000 disclose the CCR5 chemokine receptor as a valid target for developing HIV therapeutics (Proudfoot 1999, page 459, first column, last paragraph) Proudfoot 2000 discusses nonpeptidyl agents selective for CCR5 including TAK 779 from Takeda and SCH-C of Schering Plough for use in inhibiting HIV-1 infections (Proudfoot 2000, page 254, column 1). Berger 1999 also supports fusion inhibitor based therapies that target $CCR5^+$ cells as stated at page 684, paragraph 3:

> Low Molecular Weight Compounds. Perhaps the most promising class of blockers is low molecular weight compounds that bind directly to the coreceptors and inhibit their function. In general, members of the G protein-coupled receptor superfamily have proven to be ripe targets for pharmacologic intervention, and the chemokine receptors were already under investigation for development of anti-inflammatory drugs prior to their implication in HIV-1 entry.

Berger 1999 concludes on page 687, last paragraph:

> Demonstration of HIV-1 disease-modifying polymorphisms in CCR5 and other coreceptor genes represents a landmark in our understanding of the influence of human genetic factors on outcome in HIV-1 infection, and it supports genetic analysis as a general approach for understanding the heterogeneity of outcome characteristic of all infectious diseases. The observation that protective coreceptor mutations and polymorphisms are well-tolerated provides the proof of principle needed to justify development of coreceptor-based preventive and therapeutic interventions for the

AIDS epidemic, and reason for optimism that they may succeed.

Applicants submit that the cited art does not cast doubt on enablement of nonpeptidyl agents for use in a method of inhibiting HIV-1 infection as recited in the claim. Moreover, Applicants view points 5 and 6 as simply stating in a different manner the same thing the Examiner has already stated in points 1, 2 and 4, i.e., that the structure of the agents and/or the molecular determinants must be known for the method of the invention to be enabled. In response, applicants therefore respectfully reiterate their arguments set forth above. To avoid redundancy, these arguments are not repeated here. They are, however, expressly incorporated herein by specific reference thereto.

For the reasons set forth above, applicants respectfully traverse the arguments made by the Examiner in points 1-6 and submit the disclosure of their invention as set forth in their specification, coupled with the level of skill of one of ordinary skill in this art, meets if not exceeds the requirements of the factors set forth in the Court's decision in *Wands, supra*. Thus the present invention is clearly enabled in accordance with the requirements of 35 U.S.C. §112, ¶1.

The Examiner further stated on pp. 4-5 of the Office Action that applicants traverse [i.e., the rejection under §112 in their previous response filed April 8, 2002] and submit

that the claimed invention is fully supported by the disclosure. The Examiner stated that a declaration was provided by Dr. Tatjana Dragic under 37 C.F.R. §1.132 [i.e., the "prior declaration"] to further support this assertion. The Examiner stated that applicants' arguments and the declaration of Dr. Dragic have been carefully considered but are insufficient to overcome the rejection.

The Examiner then stated that while the declaration provides a generic screening assay to identify putative non-peptidyl inhibitors of HIV, applicants are reminded that the claims are directed toward methods of inhibiting HIV-1 infection of a CD4+ cell through the administration of a non-peptidyl agent. The Examiner stated that accordingly the claims encompass *in vitro*, *in vivo*, and clinical applications. The Examiner stated that however, nothing in the disclosure leads the skilled artisan to any particular class of compounds. The Examiner stated that the specification fails to provide any guidance pertaining to the molecular determinants of any given inhibitor or class of inhibitors. The Examiner stated that the specification fails to identify any putative antiviral compounds that can reasonably be expected to function *in vivo* or in the clinic. The Examiner stated that finally, nothing in the response or declaration provides any date or evidence demonstrating that obviates the large number of references cited which demonstrate how difficult it is for the skilled artisan to identify and develop novel antiviral agents. The Examiner stated that accordingly, when all the aforementioned factors are considered *in toto*, it would

clearly require undue experimentation from the skilled artisan to practice the claimed invention.

In response to the Examiner's comments noted above, applicants submit herewith as **Exhibit A** a, "Second Declaration Under 37 C.F.R. §1.132 of Tatjana Dragic" (the "Second Declaration"). Entry of this declaration into the file of the present application is respectfully requested. Notwithstanding the fact that the declaration is being submitted following the issuance of a Final Office Action, this Second declaration could not have been earlier filed. That is, it is being provided in response to the Examiner's objections concerning Dr. Dragic's first declaration (the prior declaration), which objections were set forth for the first time in the February 27, 2003 Office Action concerning this application.

Dr. Dragic's Second Declaration Under 37 C.F.R. §1.132 Fully Addresses The Examiner's Objections Concerning Her Prior Declaration

In response to the Examiner's above-noted comments concerning Dr. Dragic's prior declaration, Dr. Dragic states, in ¶5 of her Second Declaration, that based on the disclosure contained in the specification of the present application and the general knowledge in the field concerning the use of the Resonance Energy Transfer ("RET") assay as of April 2, 1996, one skilled in the art could readily, without the need for any undue experimentation, have utilized such RET assay to determine whether any given non-peptidyl agent capable of binding to a CCR5 chemokine

receptor on the surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell is capable of inhibiting the fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell, and to use an agent thus identified to inhibit such fusion in accordance with the presently claimed invention. Dr. Dragic then goes on to state (in ¶6) that such method would clearly encompass, in addition to *in vitro* applications, both *in vivo* and clinical applications of the non-peptidyl agents identified with the use of the RET assay. Dr. Dragic then reiterated her opinion, (as originally stated in ¶18 of her prior declaration), that she expects and believes, based on her extensive experience in researching anti-HIV therapies, that non-peptidyl compounds and analogs thereof that bind the CCR5 receptor of CD4+ cells and which inhibit fusion of HIV-1 or HIV-1-infected cells, as determined by the RET assay, have a reasonable probability to inhibit and treat HIV-1 infection in humans, i.e., involving both *in vivo* and clinical settings.

In support of Dr. Dragic's statements noted above, she has attached as Exhibit 1 to her Second declaration a copy of PCT International Publication No. WO 02/ 079186 A2 ("the published PCT application") entitled "Aminopiperidine Derivatives". As noted by Dr. Dragic in ¶6 of her Second Declaration, the piperidine derivatives disclosed and claimed in the published PCT application fall within the scope of the compositions taught for use in the method of the present invention, i.e., non-peptidyl compounds which prevent HIV virus from entering CD4+ cells by binding to the CCR5 receptor, optionally without blocking chemokine

binding, and thereby preventing the interaction of gp120 and CD4 with this receptor. As additionally noted by Dr. Dragic in ¶7 of her Second Declaration, the compounds disclosed and claimed in the published PCT application are those which were described in the Olson et al. abstract attached as Exhibit 3 to her prior declaration. The Olson et al. abstract was provided in support of Dr. Dragic's contention that one of ordinary skill in this art could use the RET assay method taught by applicants in their specification (see discussion below) in order to readily identify non-peptidyl compositions useful in the claimed method of the invention.

Paragraphs 8-10 of Dr. Dragic's Second Declaration establishes that: (1) the assay method used in the published PCT application to identify the (non-peptidyl) agents useful in inhibiting fusion of HIV-1 to a CD4+ cell by binding to a CCR5 receptor is that described by Litwin, V., et al. J. Virol. 70(9) 6437-6441 (1996), and (2) The RET method taught for use in applicants' specification (see, e.g., page 19, line 22- page 20, line 1) is as described in Litwin et al. The teachings contained in the published PCT application thus further support applicants' contention that one of ordinary skill in the relevant art at the time the invention was made could have readily utilized the RET assay taught in the present specification (i.e., that of Litwin, et al.) to identify nonpeptidyl compounds useful in *in vivo* and clinical applications, as well as in *in vitro* applications involving the inhibition of fusion between HIV-1 or HIV-1-infected cells and CD4+

target cells by binding to CCR5 chemokine receptors on the target cells.

Next, with regard to the Examiner's objection regarding the lack of guidance provided by applicants pertaining to the molecular determinants of any given inhibitor or class of inhibitors, Dr. Dragic points out in ¶12 of her Second Declaration that the Olson et al. abstract (discussed above) demonstrates that using the RET method of screening used by applicants in the present invention and also taught for use in the published PCT application, non-peptidyl compounds can be identified that are useful in applicants' claimed method without prior knowledge of the structures of these non-peptidyl compounds, and without the need for any undue experimentation. In her Second Declaration, Dr. Dragic reiterates the position espoused in ¶15 of her prior declaration wherein she pointed out that the Olson et al. abstract discloses that even without advance knowledge of the structure of the compounds that specifically block CCR5-mediated HIV-1 cell-cell and virus-cell-fusion, compositions, including non-peptidyl compounds, were readily defined without the need for any significant experimentation. Dr. Dragic additionally states in ¶12 of her Second Declaration that the identification of molecular determinants in unnecessary to enable one skilled in this art to identify inhibitors which will perform effectively in the method of the invention.

The Examiner in his remarks in the present Office Action stated that the specification fails to identify any

putative antiviral compounds that can reasonably be expected to function *in vivo* or in the clinic. In response, the Examiner's attention is respectfully directed to ¶¶14-17 of Dr. Dragic's Second Declaration wherein there is described antiviral compounds, identifiable through the use of the RET assay, having demonstrated *in vivo* anti-viral efficacy.

In ¶14 of her Second Declaration Dr. Dragic discusses a report based on data generated by Progenics Pharmaceuticals which demonstrates that a non-peptidyl agent produced by Schering-Plough identified as "SCH-C" (i.e., SCH 351125) inhibits, *in vitro*, HIV-1_{JR-FL} envelope-mediated fusion with PM-1 cells in the RET assay. A copy of this report is attached as Exhibit 3 to Dr. Dragic's Second Declaration. As noted in the subject exhibit, the RET assay was carried out by the Litwin, V., et al. method described in both the published PCT application (Exhibit 1 to Dr. Dragic's Second Declaration) and in the specification of the present application (see, e.g., pps. 19-20).

The *in vivo* clinical efficacy of the SCH-C composition is thereafter demonstrated pursuant to the discussion in ¶15 of Dr. Dragic's Second Declaration. As noted therein, attached as Exhibit 4 to the subject declaration is a copy of an abstract by Reynes, J., et al. entitled, "SCH C: Safety and Antiviral Effects of a CCR5 Receptor Antagonist in HIV-1 Infected Subjects." The abstract provides *in vivo* clinical data demonstrating that SCH-C reduced the viral load in HIV-1-infected humans. In particular, 10 of 12

subjects treated with this non-peptidyl agent had at least a 0.5 $\log_{10}$ reduction in viral load from baseline during dosing, with 4 subjects achieving a 1.0 $\log_{10}$ or greater reduction. As further noted by Dr. Dragic in ¶15, the authors of the abstract concluded that, based on their clinical trials, the CCR5 receptor is a viable target for antiretroviral (i.e., anti-HIV) therapy. The abstract thus further supports applicants' contention that the presently claimed invention is enabled for both *in vivo* and clinical applications, as well as for *in vitro* applications.

In ¶16 of her Second Declaration, Dr. Dragic discusses another agent (albeit not a non-peptidyl agent) identified as a fusion inhibitor using the RET assay which has demonstrated *in vivo* effectiveness in preventing fusion between HIV-1 and CD4+ cells. In this regard, Dr. Dragic has attached as Exhibit 5 to her Second Declaration a copy of an abstract by Olson, W.C., et al. entitled, "The HIV-1 Entry Inhibitor PRO 140 Potently and Durably Suppresses Viral Replication *in vitro* and *in vivo*." Dr. Dragic points out that the subject declaration provides animal data obtained with the use of a monoclonal antibody designated PRO 140 developed by Progenics Pharmaceuticals, Inc., the Assignee of the present application, that the subject antibody is capable of preventing HIV-1 fusion to CD4+ cells. As discussed in the abstract, in both single-dose and multi-dose *in vivo* treatment regimens involving SCID (severe, combined immunodeficiency) mice, the PRO 140 antibody potently and durably reduced viral levels in the mice to undetectable levels. As additionally noted by Dr.

Dragic in ¶16 of her Second Declaration, the abstract also states that the viruses remained sensitive to PRO 140 following prolonged periods of exposure both *in vitro* and *in vivo*.

Accordingly, Dr. Dragic therefore reached the conclusion, as stated in ¶16 of her Second Declaration, that the PRO 140 antibody has demonstrated potent and sustained activity against primary HIV viruses both *in vitro* and in a well-recognized model of animal infection, and that the salutary effects achieved with the use of the PRO 140 antibody serve to support the conclusion that, as a whole, the fusion inhibitor class of therapeutic compositions, identified via the RET assay taught in the present application and in Litwin et al., would likely be useful in inhibiting HIV infection in both *in vivo* and clinical settings. As further stated by Dr. Dragic in ¶17 of her Second Declaration, moreover, the results achieved with the use of the SCH-C and PRO 140 compositions further reinforces her opinion (as originally stated in ¶18 of Dr. Dragic's prior declaration) that it is her expectation and belief that non-peptidyl compounds and analogs thereof that bind the CCR5 chemokine receptor of CD4+ cells and inhibit fusion of HIV-1 or HIV-1-infected cells, as determined by the RET assay, have a reasonable probability to inhibit and treat HIV-1 infection in humans.

Further evidence in support of applicants' contention that the claimed method of the invention is enabled is provided in ¶18 of Dr. Dragic's Second Declaration. As discussed

therein, an additional assay for determining binding between HIV-1_{JR-FL} and $CCR5^+$ CD4+ cells, and, by extension, for determining the inhibitory effects on such binding of a variety of agents, is described in the Experimental Details portion of applicants' specification at pages 45 and 47-48 of the application. Attached as Exhibit 6 to Dr. Dragic's Second Declaration is a graph produced by Progenics Pharmaceuticals, Inc. illustrating the results of Progenics' in-house testing of four non-peptidyl compounds using the gp120/CCR5 binding assay method described on the above-identified pages of the specification. The exhibit graphically illustrates the degree of binding inhibition obtained with the use of TAK-779 (a product of Takeda Pharmaceuticals), the Schering Plough SCH-C composition described above in the discussion of the RET assay, and two Roche compositions, identified as "7948" and "8260" respectively, which as noted by Dr. Dragic are described in the published PCT application attached as Exhibit 1 to her Second Declaration. Thus, nonpeptidyl agents shown to inhibit fusion using the RET assay also inhibit binding of HIV-1_{JR-FL} gp120/sCD4 complexes to $CCR5^+$ cells. The gp120/CCR5 assay described by applicants on pps. 45 and 47-8 provides another methodology for determining the binding inhibition characteristics of a variety of agents shown by the RET assay to be HIV-1 fusion inhibitors, including non-peptidyl agents (as shown in the graph attached as Figure 6). This teaching therefore provides additional evidence that the disclosure contained in applicants' specification fully enables the method recited in claim 61, i.e., the sole claim pending in this application.

In ¶19 of her Second Declaration Dr. Dragic responds to the Examiner's statement on p. 5 of the Office Action to the effect that applicants have provided no data or evidence that obviates the large number of references cited which demonstrate how difficult it is for the skilled artisan to identify and develop novel antiviral agents. In response, as stated by Dr. Dragic, notwithstanding the disclosures of the cited references, simply identifying difficulties in identifying antiviral agents does not mean that such difficulties may not, and in fact, have not, been overcome.

As further noted by Dr. Dragic, on the contrary those skilled in this art expect that the development of new technologies and approaches, i.e., as described in the present application and as further supported by the data presented in her Second Declaration, serve to overcome these difficulties.

Further concerning the references noted by the Examiner in points 5 and 6 discussed above, applicants respectfully submit that, as discussed more fully below, they are of the belief that they are entitled to a priority date of at least June 13, 1997 for the present invention. Thus the references cited in the Examiner's point no. 5, having effective dates in 1999 and 2000, are not prior art to the claimed invention.

Further, as pointed out on pps. 8-9 of applicants' previous Amendment filed April 8, 2002, claim 61 recites the use of

a non-peptidyl compound to bind the CCR5 chemokine receptor. There is no requirement that the non-peptidyl inhibitor have a broad range of reactivity to all chemokine receptors. Moreover, the inhibitor, being non-peptidyl in nature, has little if any likelihood of being immunogenic.

As also noted in applicants' previous response, in terms of a non-peptidyl agent having utility as a therapeutic, Dr. Dragic, as one skilled in the field of HIV-1 research, has an expectation and belief (as stated in ¶18 of her prior declaration) that non-peptidyl compounds and analogs thereof that bind the CCR5 chemokine receptor of CD4+ cells and inhibit fusion of HIV-1 or HIV-1-infected cells as determined, e.g., by the RET assay, have a reasonable probability to inhibit and treat HIV-1 infection in humans.

AS applicants additionally pointed out in their April 8, 2002 response, the Examiner also cites (in point no. 6) to other prior art as a basis for doubting the utility of the method of inhibiting HIV-1 infection. In so doing, the Examiner relies particularly on Gait and Karn (1995) as summarizing the prior art, which reference relates to protease inhibitors as antiviral drugs. In response to such reliance by the Examiner, applicants reiterate their previously-stated position (see prior Amendment, p. 9) that the subject prior art is not germane to the present invention, i.e., the present invention is not a protease inhibitor. Any difficulties encountered in the development of a protease inhibitor as a clinical therapeutic are not applicable to the use of a non-peptidyl agent that binds a

CCR5 chemokine receptor on CD4+ cells and thus inhibits fusion with HIV-1 or an HIV-1-infected cell.

Dr. Dragic accordingly has concluded in ¶19 of her Second Declaration that, as demonstrated by the evidence provided in the two declarations she has provided in this application, one of ordinary skill in this art, relying on the teachings of the present specification taken together with the general knowledge in the field as of April 2, 1996, would be readily enabled to practice the claimed method of the invention.

In summary, therefore, the Examiner's objections to Dr. Dragic's prior declaration as set forth on page 5 of the present Office Action are respectfully traversed for the reasons set forth above, which reasons summarize the arguments made in response to these objections by Dr. Dragic in her Second Declaration provided in this application.

35 U.S.C. §120

The Examiner further stated in the Office Action (see ¶5 on p.5) that as previously set forth, applicants' claim for domestic priority under 35 U.S.C. §119(e) and 120 was acknowledged. The Examiner stated that however, the applications upon which priority is claimed fail to provide adequate support under 35 U.S.C. §112 for claims 61 and 65 of this application. The Examiner stated that these earlier applications relied upon fail to provide adequate support for non-peptidyl inhibitory agents that are not of

the bicyclam family. The Examiner stated that accordingly, for the purposes of applying prior art, the effective filing date of the instant application will be 12 December, 1998.

In response, the Examiner's attention is respectfully directed to the fact that, as pointed out on page 10 of applicants' Amendment filed April 8, 2002 in response to the October 2, 2001 Office Action, claim 65 was cancelled and claim 61 of this application, i.e., the only claim still pending in this case, was amended in the prior response to **delete** the recitation of the negative limitation, i.e., that the non-peptidyl agent not be a bicyclam or a derivative thereof. Therefore, the subject limitation is **not included** in claim 61 of this application.

Applicants thus reiterate their argument (originally made in their prior response) that support for the invention **as set forth in claim 61** (i.e., which does not include the negative limitation) is present at least as far back as applicants' application Serial No. 08/876,078 filed June 13, 1997 for the reasons provided below. Applicants therefore submit that the effective filing date for the claim of the instant application should thus be at least the June 13, 1997 filing date of the 08/876,078 application.

As noted above claim 61 recites a method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with a non-peptidyl agent, said nonpeptidyl agent

capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection. As set forth, for example, at p. 4, lines 8-13 of the 08/876,078 application, the specification states:

> This invention also provides a method for inhibiting HIV-1 infection of CD4+ cells which comprises contacting CD4+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4+ cells is inhibited, thereby inhibiting the HIV-1 infection.

On the same page, at lines 23-24, the specification goes on to state that, "In a separate embodiment, the agent is a nonpeptidyl agent."

Still further, on p.12 at lines 16-20, the specification teaches:

> A chemokine receptor means a receptor capable of binding RANTES, MIP-1α, MIP-1β or another chemokine which blocks HIV-1 infection. Such chemokine receptor includes but [is] not limited to CCR5, CXCR4, CCR4 and CCR-2B.

Further to the above, applicants note that in the present response, claim 61 has been further amended to recite that the agent is capable of binding to a CCR5 chemokine receptor, "[o]n the surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell." As support for the subject amendment applicants cited to pps. 31-36 of the present application, and particularly Table 1 on page 32 and Table 2 on page 35. Applicants submit that

the above-identified pages correspond exactly to pages 30-36 of application Serial No. 08/876,078 (except due to spacing differences in the text, Table 1 appears on page 31 while Table 2 has shifted to page 34). Thus the earlier '078 application also supports the amendment made to claim 61 in the present response.

As demonstrated above, therefore, the teachings of application Serial No. 08/876,078 completely support the presently claimed invention as now recited in (amended) claim 61. Thus the effective filing date for the claim of the instant application should be at least June 13, 1997, filing date of application Serial No. 08/876,078. The Examiner is therefore respectfully requested to reconsider and withdraw his refusal to grant applicants the benefit of the priority of their prior application Serial No. 08/876,078.

Rejection Under 35 U.S.C. §102(a)

The Examiner stated in ¶7 on p. 6 of the Office Action that claim 61 stands rejected under 35 U.S.C. §102(a) as being anticipated by *Howard et al.* (1998). The Examiner stated that this teaching describes a method for inhibiting HIV-1 infection of CD4+ cells through the administration of a non-peptidyl agent (e.g., NSC651016, a distamycin analog) that binds to a chemokine receptor (e.g., CCR5, CXCR4) and is not a bicyclam or a derivative thereof (see Results, pp. 8-10). The Examiner stated that this teaching clearly meets all of the claimed limitations. The Examiner stated that

applicants' amendment and arguments fail to obviate the rejection for the reasons of record.

Applicants respectfully traverse this rejection for the reasons which follow.

First, as pointed out above, applicants amended claim 61 in their previous response filed in this case to delete the negative limitation from the claim. Thus the subject claim no longer recites the language "provided that the nonpeptidyl agent is not a bicyclam or derivatives thereof. Second, as further demonstrated above claim 61, without the negative limitation, is entirely supported by the teaching of applicants' earlier application Serial No. 08/876,078 filed June 13, 1997 and thus the effective filing date of the subject claim with respect to the prior art should be at least June 13, 1997.

As stated in applicants' prior response, therefore, in contrast to the June 13, 1997 date to which applicants' claim is entitled, the Howard et al. reference cited to reject the claim has an effective date as a reference of June, 1998. This June, 1998 reference date is over one year after the due date to which the subject matter of claim 61 is entitled for the reasons set forth above. Therefore, the Howard, et al. reference is **not** prior art to the invention as presently claimed and the Examiner is thus respectfully requested on that basis to reconsider and withdraw the rejection under §102(a) based on the subject reference.

Notwithstanding the arguments set forth above, however, and without conceding the correctness of the position espoused by the Examiner (i.e., that the Howard, et al. reference is a valid prior-art reference against claim 61), applicants, in an attempt to expedite the prosecution and eventual allowance of this application, have amended claim 61 herein to further distinguish the invention over the disclosure contained in the subject reference.

As discussed *infra*, claim 61 of the application has been amended to recite that the nonpeptidyl agent is capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell. In contrast, however, the Howard et al. reference describes a method for inhibiting HIV-1 infection of CD4+ cells through the administration of a non-peptidyl agent, i.e., NSC 651016 (a distamycin analog) that binds to both CCR5 **and** CXCR4 receptor sites. As stated, for example on page 9 of the reference:

Thus, NSC 651016 mediates its antiviral effects through interference with both the monocyte-tropic (CCR5) and lymphocyte-tropic (CXCR4) chemokine co-receptors (see col. 2, lines 1-4).

The authors of the reference then additionally stated, on p. 10, col. 2 in the first paragraph of the "Discussion":

We have demonstrated that NSC 651016, a small molecular inhibitor of HIV-1 replication *in vivo* and *in vitro*, acts by interfering with a stage of virus infection between CD4-gp120 binding and fusion with target cells. We have also shown that NSC 651016 inhibits RANTES, MIP-1α and MIP-1β to CCR5 and SDF-1α binding to CXCR4 . . ..

Thus, notwithstanding that it has been established above that Howard et al. is not prior art to the invention as presently claimed, the invention as recited in claim 61 is, moreover, completely distinguishable over the subject reference since the agents determined by the method of the present invention bind to a CCR5 receptor on a PM-1 cell but not to a CXCR4 receptor on such PM-1 cell, whereas the NSC 651016 small molecule disclosed in Howard et al. binds to both the CCR5 and the CXCR4 receptors. For this reason as well, the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 61 under 35 U.S.C. §102(a) over Howard et al.

Summary

For all of the reasons set forth hereinabove, applicants submit that the invention recited in claim 61 is described in the present specification in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. Moreover, applicants have conclusively demonstrated that their claimed invention is entitled to an effective date of at least June 13, 1997, which pre-dates the effective date of the Howard et al reference, and thus Howard et al. is not prior art to the present invention. Notwithstanding the inapplicability of Howard et al. as a reference against the invention, applicants have amended the claim of the application to further distinguish it over the disclosure of the subject reference. Applicants thus respectfully request that the Examiner reconsider and

withdraw the various grounds of rejection and earnestly solicit allowance of claim 61 now pending in the application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examine to telephone either of them at the number provided below.

A fee of $465.00 for a three-month extension of time is deemed necessary in conjunction with the filing of this response and a check for this amount is enclosed. If any additional fee is due, authorization is hereby given to charge the required fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Mark A. Farley 6/27/05

John P. White Date
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Dkt. 50875-F-PCT-US/JPW/MAF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Graham P. Allaway, t al.
U.S. Serial No.:		09/460,216 Examiner: J. Parkin
Filed	:	December 13, 1999 Group Art Unit: 1648
For	:	METHODS FOR PREVENTING HIV-1 INFECTION OF CD4+ CELLS

1185 Avenue of the Americas
New York, New York 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

SECOND DECLARATION UNDER 37 C.F.R. §1.132 OF TATJANA DRAGIC

I, Tatjana Dragic, Ph.D, hereby declare that:

1. I am the same Tatjana Dragic who provided the "Declaration Under 37 C.F.R. §1.132 of Tatjana Dragic" executed on March 31, 2002 ("prior declaration"). I understand that my prior declaration was appended as an Exhibit to an Amendment filed April 2, 2002 by applicants' Counsel in support of the patentability of the claim of this application.

2. I have read and am familiar with the Office Action dated February 27, 2003 from the Patent and Trademark Office Examiner in charge of this application. In particular, I have read and am familiar with the Examiner's comments on pages 4-5 of the Office Action regarding my prior declaration. The following remarks are provided in response to the Examiner's comments concerning my prior declaration in the February 27, 2003 Office Action.

3. I understand the invention as presently claimed to be directed to a method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with a nonpeptidyl agent, said nonpeptidyl agent capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell, but not to a CXCR4 receptor on the surface of such PM-1 cell, in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

4. On page 5 of the February 27, 2003 Office Action, the Examiner stated that while my prior declaration provides a generic screening assay to identify putative non-peptidyl inhibitors of HIV, the claim of the application is directed toward a method of inhibiting HIV-1 infection of a CD4+ cell through the administration of a non-peptidyl agent, and accordingly, the claim encompasses *in vitro*, *in vivo* and clinical applications. The Examiner then stated that nothing in the disclosure leads the skilled artisan to any particular class of compounds.

5. As stated in ¶7 of my prior declaration, however, based on the disclosure contained in the specification of the present application and the general knowledge in the field concerning the use of the Resonance Energy Transfer (RET) assay as of April 2, 1996, one skilled in the art could readily, without the need for any significant, i.e., undue, amount of experimentation, have utilized such RET assay to determine whether any given non-peptidyl agent (which is capable of binding to

a CCR5 ch mokine r ceptor on th surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell) is capable of inhibiting the fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell, and to use an agent thus identified to inhibit such fusion in accordance with the presently claimed invention. Clearly this would encompass, in addition to *in vitro* applications, both *in vivo* and clinical applications of the non-peptidyl agents identified through the use of the RET assay. Moreover, as I additionally stated in ¶18 of my prior declaration, it is my expectation and belief, based on my extensive experience in researching anti-HIV therapies, that non-peptidyl compounds and analogs thereof that bind the CCR5 chemokine receptor of CD4+ cells and inhibit fusion of HIV-1 or HIV-1-infected cells as determined by the RET assay, have a reasonable probability to inhibit and treat HIV-1 infection in humans, i.e., in both *in vivo* and clinical settings.

6. As evidence in support of the statements in ¶5 above, I attach hereto as **Exhibit 1** a copy of PCT International Publication No. WO 02/079186 A2 ("the published PCT application") entitled, "Aminopiperidine Derivatives", published October 10, 2002. As noted on page 1, lines 2-10 of the published PCT application, the invention described therein relates to compounds which are piperidine derivatives and to the use of such compounds to prevent the human immunodeficiency virus (HIV) from entering cells by blocking interactions of the viral envelope protein gp120 with a chemokine receptor on the cell surface. As described, for example, on page 2, lines 11-15 of the published PCT application, the

inv ntion describ d ther in has as its obj ct th provision of compounds which inhibit entry of HIV into target cells by binding to the CCR5 receptor, optionally without blocking chemokine binding, and thereby preventing the interaction of HIV gp120 and CD4 with this receptor. The published PCT application additionally states that these compounds show a great potential to be efficacious in the prevention and treatment of HIV-related diseases.

7. Attached as Exhibit 3 to my prior declaration was an Abstract by Olson, et al., of which I am a co-author, entitled, "Identification of CCR5 Coreceptor Inhibitors That Potently and Selectively Block HIV-1 Replication." As discussed in ¶¶14-16 of the subject declaration and as set forth in the Results section of the Olson et al. Abstract, nonpeptidyl compounds were identified with the use, *inter alia*, of the RET screening assay which specifically blocked CCR5- mediated, but not CXCR4-mediated HIV-1 cell-cell and virus-cell fusion. It is these compounds which are used in the method of the present invention as described above in ¶3. The Olson et al. Abstract was a joint presentation of Progenics Pharmaceuticals, Inc., to which the present application is assigned, the Albert Einstein College of Medicine, Bronx, NY, by which I am employed and Roche Discovery of Palo Alto, CA. The compounds which were described in the Olson et al. Abstract are now described and claimed in the published PCT application.

8. The sole fusion assay method by which the compounds described and claimed as having utility for inhibiting

fusion of HIV to a CD4+ cell in the published PCT application is identified on page 61 of the publication as being the RET assay as described in Litwin, V., et al. (1996), "Human Immunodeficiency Virus Type 1 Membrane Fusion Mediated By A Laboratory-Adapted Strain And A Primary Isolate Analyzed By Resonance Energy Transfer", J. Virol. 70(9):6437-6441 ("Litwin, et al."). A copy of the Litwin et al. article is attached hereto as **Exhibit 2.** The assay is described, *inter alia*, in col. 2 on p. 6437 of the article, at lines 3-18. The authors state that this fluorescence-based technique involves labeling one fusion partner (an HIV-1 gp120/gp41-expressing cell line) with fluorescein octadecyl ester (F18) and the other fusion partner (a CD4-expressing cell line) with octadecyl rhodamine (R18). The article states further that the flurochromes are chosen such that the emission spectrum of one (F18) overlaps the excitation spectrum of the second (R18) and that fusion results in the close association of the dyes in the plasma membrane, thus transfer of the energy generated by F18 excitation to R18 is followed by emission at the R18 spectrum. The article then goes on to describe (see pps. 6440-1) the determination of membrane fusion inhibition with the use of the subject RET assay, wherein the fusion-inhibition characteristics of several agents, including antibodies such as OKT4A and fusion proteins such as CD4-IgG2, are demonstrated.

9. As discussed in my prior declaration (see ¶¶9-12) the specification of the present application provides substantial disclosure, and a significant degree of guidance, regarding the RET assay used for determining

cell fusion and thus for calculating the degree of inhibition of such fusion provided by a variety of different agents, including nonpeptidyl agents which are the subject of the present invention. A detailed description of the RET assay as used in the present invention is provided, e.g. at from page 19, line 22 to page 20, line 1 of the specification. As taught therein by the applicants, the RET assay may be used, *inter alia*, for determining whether a non-chemokine agent (defined in the specification as including nonpeptidyl agents) is capable of inhibiting the fusion of HIV-1 to a CD4+ cell. The method comprises (a) contacting (i) a CD4+ cell labeled with a first dye; and (ii) a cell expressing the HIV-1 envelope glycoprotein on its surface, which is labeled with a second dye, in the presence of an excess of the agent under conditions permitting the fusion of the CD4+ cell to the cell expressing the HIV-1 envelope glycoprotein on its surface, in the absence of the agent, wherein the first and the second dyes are selected so as to allow resonance energy transfer between the dyes. The product of the contacting step described above is then exposed to conditions that would result in resonance energy transfer if fusion has occurred. In a further step, the RET assay method then involves making a determination whether there is a reduction in resonance energy transfer when compared with the resonance energy transfer which is obtained in the absence of the agent. A decrease in the resonance energy transfer thus indicates that the agent is capable of inhibiting fusion.

10. A comparison of the Litwin et al. RET assay m thod described in ¶8 above with the methodology described by the applicants in their specification (¶9 above) clearly evidences that the RET assay method described in Litwin et al., i.e., which as noted above is used in identifying fusion-inhibiting nonpeptidyl compounds described in the published PCT application (Exhibit 1), is as taught by applicants for use in identifying fusion inhibiting compounds (peptidyl and nonpeptidyl) useful in the method of the present invention.

11. Further to the above, the published PCT application (Exhibit 1) states on page 59, lines 27-33, that the compounds described by the publication, and pharmaceutical compositions containing the same, are useful for the treatment of diseases mediated by retroviruses, such as the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV replication (see also, page 59, line 18 to page 60, line 5 and page 64, line 1 to page 65, line 20). The published PCT application thus demonstrates that the skilled artisan may, by the use of the RET assay taught for use in the present application, readily identify without any undue experimentation non-peptidyl agents which inhibit fusion between HIV and CD4+ cells and having both *in vivo* and clinical applications. It is also my view that the reliance by the published PCT application on the RET assay is a validation and acceptance by the skilled artisan of the teachings of the present specification that nonpeptidyl fusion inhibitors identified by the RET assay have a

r asonable probability of having *in vivo* and clinical efficacy.

12. On page 5 of the February 27, 2003 Office Action concerning this application, the Examiner additionally stated that applicants' specification fails to provide any guidance pertaining to the molecular determinants of any given inhibitor or class of inhibitors. As pointed out in my prior declaration (see, e.g., ¶¶15-17), the Olson et al. abstract (Exhibit 3 thereto) demonstrates that, using the RET method of screening, as also disclosed in the present application, non-peptidyl compounds were identified that are useful in the method claimed as applicants' invention without prior knowledge of the structures of these non-peptidyl compounds and without the need for any significant, i.e., undue, amount of experimentation. In particular, as stated in ¶15 of my prior declaration, the Olson et al. abstract discloses that even without advance knowledge of the structure of the compounds that specifically block CCR5-mediated, but not CXCR4-mediated HIV-1 cell-cell and virus-cell-fusion, compositions, including non-peptidyl compounds, were readily defined without the need for any significant amount of experimentation. Thus the identification of molecular determinants is unnecessary to enable one skilled in this art to identify inhibitors and/or classes of inhibitors which will perform effectively in the method of the invention.

13. The Examiner additionally stated on page 5 of the February 27, 2003 Office Action that the specification fails to identify any putative antiviral compounds that

can r asonably b xpected to function *in vivo* or in the clinic. In response, the discussion in ¶¶14-15 below is directed to a product of the Schering-Plough Corporation designated SCH-C which is a non-peptidyl antiviral compound that, in accordance with the presently claimed method, has demonstrated therapeutic utility in inhibiting HIV infections as demonstrated through the used of the RET assay.

14. Attached hereto as **Exhibit 3** is a report based on data generated by Progenics Pharmaceuticals, Inc., the Assignee of the present application, which demonstrates that the Schering-Plough non-peptidyl agent SCH-C (i.e., SCH 351125) inhibits, *in vitro*, HIV-1_{JR-FL} envelope-mediated fusion with PM-1 cells in the RET assay. As noted in the report, the RET assay was carried out by the method (i.e., that of Litwin, V., et al. 70:6437 (1996)) described in both the published PCT application (see ¶8) and in the specification of the present application (see ¶9). The Schering-Plough non-peptidyl SCH-C product was tested for inhibition of HIV-1_{JR-FL} envelope-mediated membrane fusion. The IC50, i.e., the concentration of SCH-C required to inhibit such HIV-1 fusion by 50%, was found to be 12nM.

15. Attached hereto as **Exhibit 4** is a copy of an abstract by Reynes, J., et al. entitled, "SCH C: Safety and Antiviral Effects of a CCR5 Receptor Antagonist in HIV-1 Infected Subjects" (Abstract 1). This abstract was presented at the 9th Conference on Retroviruses and Opportunistic Infections. As pointed out in the abstract, SCH-C is an orally bioavailable CCR5 receptor antagonist with potent *in vitro* antiviral activity

against a broad selection of primary HIV-1 isolates. The abstract provides *in vivo* clinical data demonstrating that SCH-C reduced the viral load in HIV-1 infected humans. That is, 10 of 12 subjects treated with this non-peptidyl agent had at least a 0.5 $\log_{10}$ reduction in viral load from baseline during dosing, with 4 subjects achieving a 1.0 $\log_{10}$ or greater reduction. The authors concluded that, based on the above-described clinical trials, the CCR5 receptor is a viable target for antiretroviral (i.e., anti-HIV) therapy, thus further supporting the contention that the presently claimed invention of inhibiting HIV-1 infection is enabled for both in vivo and clinical applications.

16. Another agent identified using the RET assay as described in the present application and demonstrating *in vivo* effectiveness in preventing fusion between HIV and CD4+ cells is described in an abstract attached hereto as **Exhibit 5**. The Abstract by Olson, W.C., et al., entitled "The HIV-1 Entry Inhibitor PRO 140 Potently and Durably Suppresses Viral Replication *in vitro* and *in vivo*" provides animal data, obtained with the use of a monoclonal antibody designated PRO 140 developed by Progenics Pharmaceuticals, Inc., the Assignee of the present application, to prevent HIV fusion to CD4+ cells. The abstract discloses that in both single-dose and multi-dose *in vivo* treatment regimens involving SCID (severe, combined immunodeficiency) mice, the PRO 140 antibody potently and durably reduced viral levels in the mice to undetectable levels. The abstract additionally states that the viruses remained sensitive to PRO 140 following

prolonged periods of exposure both *in vitro* and *in vivo*. PRO 140 has thus demonstrated potent and sustained activity against primary HIV viruses both *in vitro* and in a well-recognized model of animal infection. Although PRO 140 is not a non-peptidyl agent, the salutary effects achieved with the use of the subject antibody serve to support the conclusion that, as a whole, the fusion inhibitor class of therapeutic compositions (peptidyl and nonpeptidyl agents) identified via the RET assay taught in the present application is effective in inhibiting HIV infection in both *in vivo* and clinical settings.

17. The data presented in **Exhibits 3-5** as discussed in ¶¶14-16 above thus conclusively demonstrates that at least two presently known antiviral agents, i.e., SCH-C and PRO 140, may reasonably be expected to function *in vivo* and in the clinic in preventing fusion between the HIV virus and CD4+ cells targeted by the virus. Again, this further reinforces my statement in ¶18 of my prior declaration that it was my expectation and belief that nonpeptidyl compounds and analogs thereof that bind the CCR5 chemokine receptor of CD4+ cells and inhibit fusion of HIV-1 or HIV-1 infected cells as determined by the RET assay have a reasonable probability to inhibit and treat HIV-1 infection in humans.

18. Further to the discussion above concerning the RET assay, applicants additionally describe in the Experimental Details portion of their application, in particular at pps. 45-48 describing the Fourth and Fifth Series of Experiments, an assay for determining binding

betw n HIV-1_{JR-FL} /sCD4 and CCR5+ CD4- cells. As noted, e.g., at lines 16 and 32-35 on p. 45 of applicants' specification, this assay has been adapted for drug screening purposes and with the use of this assay the inhibitory effects of a variety of agents has been determined. Attached hereto as **Exhibit 6** is a graph produced by Progenics Pharmaceuticals, Inc. illustrating the results of Progenics' in-house testing of four nonpeptidyl compounds which were shown to inhibit binding in the gp120/CCR5 binding assay described at pps. 45 and 47-48 of the application. The exhibit graphically illustrates the degree of binding inhibition obtained with various concentrations of the indicated compounds. The compound identified as "TAK-779" is produced by Takeda Pharmaceuticals. "SCH-C" is the Schering-Plough material discussed above in ¶¶14-15. The two remaining compositions, designated "7948" and "8260", respectively, are produced by Roche and are described in the published PCT application (Exhibit 1). Thus, non-peptidyl agents shown to inhibit fusion using the RET assay also inhibit binding of HIV-1_{JR-FL} gp120/sCD4 complexes to CCR5+ cells. The gp120/CCR5 binding assay is thus a method taught by applicants in their specification for determining the binding inhibiting characteristics of a variety of agents, including the nonpeptidyl agents represented in Exhibit 6.

19. The Examiner additionally stated on page 5 of the February 27, 2003 Office Action that nothing in the declaration provides any data or evidence that obviates the large number of references cited which demonstrate

how difficult it is f r the skilled artisan to identify and develop novel antiviral agents. I have read and am familiar with the references cited by the Examiner including: Oberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997; Proudfoot et al 1999; Proudfoot et al 2000; and Berger et al 1999. Notwithstanding the disclosures of the cited references, I note that simply identifying difficulties in identifying antiviral agents does not mean that such difficulties may not, and in fact, have not, been overcome. On the contrary, those skilled in this art expect that the development of new technologies and approaches, i.e., as described in the present application and supported by the data discussed herein, serve to overcome these difficulties. Moreover, I submit that as clearly demonstrated by the evidence presented in my two declarations, one of ordinary skill in this art, relying on the teachings of the present specification taken together with the general knowledge in the field as of April 2, 1996, would be readily able to practice the claimed method which involves inhibiting HIV-1 infection of a CD4+ cell, which method comprises contacting the CD4+ cell with a non-peptidyl agent, said non-peptidyl agent capable of binding to a CCR5 chemokine receptor on the surface of a PM-1 cell but not to a CXCR4 receptor on the surface of such PM-1 cell, in an amount and under conditions such that fusion of HIV-1 or an HIV-1-infected cell to the CD4+ cell is inhibited, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

I hereby declare that the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Aug 26, 2003

T. Dragic

Tatjana Dragic, Ph.D.

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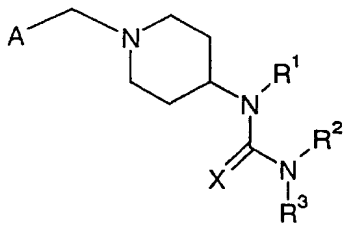
(54) Title: AMINOPIPERIDINE DERIVATIVES



(I)

(57) Abstract: The invention is concerned with novel aminopiperidine derivatives, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine. In particular, the compounds of Formula (I) prevent the human immunodeficiency virus (HIV) from entering cells by blocking interaction of the viral envelope protein gp120 with a chemokine receptor on the cell surface. Consequently the compounds of this invention may be advantageously used as therapeutic agents for the treatment of diseases mediated by the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV viral replication or with pharmacoenhancers. Disclosed are compounds of general formula (I) wherein R^1, R^2, R^3, X and A are as defined in the description.

Aminopiperidine Derivatives

The invention is concerned with novel aminopiperidine derivatives, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine. In particular, the compounds prevent the human immunodeficiency virus (HIV) from entering cells by blocking interaction of the viral envelope protein gp120 with a chemokine receptor on the cell surface. Consequently the compounds of this invention may be advantageously used as therapeutic agents for the treatment of diseases mediated by the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV replication or with pharmacoenhancers such as cytochrome P450 inhibitors.

HIV is the causative agent of acquired immunodeficiency syndrome (AIDS), a disease characterised by the destruction of the immune system, particularly of the $CD4^+$ T-cell, with attendant susceptibility to opportunistic infections. HIV infection is also associated with a precursor AIDS-related complex (ARC), a syndrome characterised by symptoms such as persistent generalised lymphadenopathy, fever and weight loss.

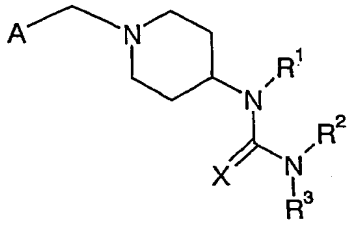
It has been reported [Liu et al., Cell 86, 367-377 (1996); Samson et al., Nature 382, 722-725 (1996); Dean et al., Science 273, 1856-1862 (1996)] that individuals who are homozygous for a deletion mutation in the CCR5 gene are highly resistant to infection by HIV, and that individuals heterozygous for this mutation have slowed disease progression [Huang et al., Nature Medicine 2, 1240-1243 (1996); Dean et al., Science 273, 1856-1862 (1996)]. Infection by HIV begins with attachment of the virus to a target cell, a process that requires the interaction of gp120 with both CD4 and a chemokine receptor (also termed a coreceptor) on the cell surface. Two important coreceptors for HIV infection are CXCR4 [Feng et al., Science 272, 872-877 (1996); Berson et al J Virol 70, 6288-6295 (1996)] and CCR5 [Alkhatib et al., Science 272, 1955-1958 (1996); Dragic et al., Nature 381, 667-673 (1996); Deng et al., Nature 381, 661-666 (1996)]. It is believed that binding to CD4 causes a conformational change in gp120 which then allows binding to the chemokine receptor [Deng et al., Nature 381, 661-666 (1996)]. Although many chemokine

receptors can serve as coreceptors for HIV in vitro, it is believed that the major coreceptor involved in sexual, parenteral and vertical transmission of HIV is the CCR5 receptor [van't Wout et al., J. Clin. Invest. 94, 2060-2067 (1994); Cornelissen, et al J.Virol. 69, 1810-1818 (1995); Veenstra et al., Clin. Infect. Dis. 21, 556-560 (1995)]. Viruses that use CCR5 as coreceptor have been termed R5 viruses, and it is believed that these are the key pathogenic strains of HIV in the majority of patients. Thus, blocking the interaction of HIV with CCR5 should prevent HIV infection of healthy individuals and should slow or halt viral spread and disease progression in infected individuals.

Cyclic amine derivatives are described in WO 99/38514 modulators of chemokine receptor activity.

The object of the invention, therefore, is to provide novel compounds which inhibit entry of HIV into target cells by binding to the CCR5 receptor, optionally without blocking chemokine binding, thereby preventing the interaction of HIV gp120 and CD4 with this receptor, and, accordingly, show a potential to be efficacious in the prevention and treatment of HIV-related diseases.

This object is achieved with the novel compounds of general formula I



I

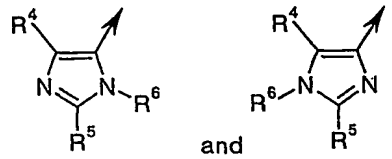
wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

X is S or O;

A is selected from the group consisting of:



A1 and A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, CN, COR, CO_2R, CONRR', NHCOR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR';

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, halogen, COR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR';

R^6 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{3-8}-cycloalkyl, COR, CO_2R, CONRR', NHCOR, SO_2NRR' or SO_2R;

R and R' are independently of each other hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

as well as ethers or hydrolyzable esters of compounds of formula I and pharmaceutically acceptable salts thereof.

The term "alkyl" as used herein, and if not specified by the number of carbon atoms, denotes an optionally substituted straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl including their different isomers. The term "C_{1-12}-alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms as defined above. The term

"C_{1-7}-alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms and more preferably the term "C_{1-4}-alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 4 carbon atoms.

Suitable substituents for the alkyl group are 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens; in case more than one substituent is attached to the alkyl group, these substituents can be identical or different from each other. Preferred substituents for the alkyl groups are 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl, substituted heterocyclyl and halogen; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens. More preferred substituents for the alkyl groups are 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl, substituted phenyl and substituted pyridyl, wherein substituted phenyl and substituted pyridyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens.

The substituents for substituted alkyl group are specifically defined below.

Alkyl in R^1 is preferably a straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms as defined above. Preferred alkyl groups in R^1 are straight or branched chain hydrocarbon residues containing 1 to 7 carbon atoms and, more preferably, the alkyl group in R^1 is methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert.-butyl.

Alkyl in R^2 and R^3 are, independently of each other, a straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms, as defined above. Preferred alkyl groups in R^2 and R^3 are straight or branched chain hydrocarbon residues containing 1 to 7 carbon atoms, and more preferred alkyl groups in R^2 and R^3 are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert.-butyl.

Alkyl in R^4, R^5, R^6, R and R' (independently of each other) denotes an optionally substituted straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl including their different isomers. Preferably, alkyl denotes a straight or branched chain hydrocarbon residue

containing 1 to 7 carbon atoms and more preferably alkyl denotes a straight or branched chain hydrocarbon residue containing 1 to 4 carbon atoms.

Alkyl in R^7 and R^8 are, independently of each other, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert.-butyl.

The term "cycloalkyl" as used herein, and if not specified by the number of carbon atoms, denotes a cycloalkyl group containing 3 to 8 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

Cycloalkyl in R^1 is as defined above, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Cycloalkyl in R^2 and R^3 (independently of each other), are as defined above, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Cycloalkyl in R^4, R^5, R^6, R and R' (independently of each other) are as defined above, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "substituted C_{1-4}-alkyl" as used herein denotes a C_{1-4}-alkyl group which is substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl or substituted heterocyclyl, wherein the substituents in substituted aryl or substituted heterocyclyl are 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents, more preferably 1 substituent selected from C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are independently of each other as defined below). Preferably, the term "substituted C_{1-4}-alkyl" as used herein denotes a C_{1-4}-alkyl group substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl, wherein substituted aryl and substituted heterocyclyl are aryl or heterocyclyl are substituted with 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents, more preferably 1 substituent selected from C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens. The term C_{1-4}-alkyl group as used herein denotes a C_{1-4}-alkyl as defined above, preferably a C_{1-2}-alkyl group, which is substituted with the aforementioned substituents; in case more than one substituent is attached to the C_{1-4}-alkyl group, these substituents can be identical or different from each other. Preferred substituents are aryl, heterocyclyl, substituted aryl or substituted heterocyclyl, more preferred substituents are phenyl, pyridyl, substituted phenyl or substituted pyridyl, wherein these substituents are substituted as mentioned above. Examples are cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,

cyclohexylmethyl, 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 2-pyridylbutyl, methyl-2-pyridyl-methyl, methyl-2-pyridyl-ethyl, dimethyl-2-pyridyl-methyl, ethyl-2-pyridyl-methyl, methoxy-2-pyridyl-methyl, methoxy-2-pyridyl-ethyl, dimethoxy-2-pyridyl-methyl, fluoro-2-pyridyl-methyl, difluoro-2-pyridyl-methyl, chloro-2-pyridyl-methyl, chloro-2-pyridyl-ethyl, dichloro-2-pyridyl-methyl, dichloro-2-pyridyl-methyl, bromo-2-pyridyl-methyl, dibromo-2-pyridyl-methyl, 3-pyridyl-methyl, 3-pyridyl-ethyl, 3-pyridyl-propyl, 3-pyridyl-butyl, methyl-3-pyridyl-methyl, methyl-3-pyridyl-ethyl, dimethyl-3-pyridyl-methyl, ethyl-3-pyridyl-methyl, methoxy-3-pyridyl-methyl, methoxy-3-pyridyl-ethyl, dimethoxy-3-pyridyl-methyl, fluoro-3-pyridyl-methyl, difluoro-3-pyridyl-methyl, chloro-3-pyridyl-methyl, chloro-3-pyridyl-ethyl, dichloro-3-pyridyl-methyl, dichloro-3-pyridyl-methyl, bromo-3-pyridyl-methyl, dibromo-3-pyridyl-methyl, 4-pyridyl-methyl, 4-pyridyl-ethyl, 4-pyridyl-propyl, 4-pyridyl-butyl, methyl-4-pyridyl-methyl, methyl-4-pyridyl-ethyl, dimethyl-4-pyridyl-methyl, ethyl-4-pyridyl-methyl, methoxy-4-pyridyl-methyl, methoxy-4-pyridyl-ethyl, dimethoxy-4-pyridyl-methyl, fluoro-4-pyridyl-methyl, difluoro-4-pyridyl-methyl, chloro-4-pyridyl-methyl, chloro-4-pyridyl-ethyl, dichloro-4-pyridyl-methyl, dichloro-4-pyridyl-methyl, bromo-4-pyridyl-methyl, dibromo-4-pyridyl-methyl, phenylmethyl (benzyl), phenylethyl, phenylpropyl, phenylbutyl, 2-methylphenylmethyl, 3-methylphenylmethyl, 4-methylphenylmethyl, 2-methylphenylethyl, 3-methylphenylethyl, 4-methylphenylethyl, 2,3-dimethylphenylmethyl, 2,4-dimethylphenylmethyl, 2,5-dimethylphenylmethyl, 2,6-dimethylphenylmethyl, 3,4-dimethylphenylmethyl, 3,5-dimethylphenylmethyl, 3,6-dimethylphenylmethyl, 2-ethylphenylmethyl, 3-ethylphenylmethyl, 4-ethylphenylmethyl, 2,3-diethylphenylmethyl, 2,4-diethylphenylmethyl, 2,5-diethylphenylmethyl, 2,6-diethylphenylmethyl, 3,4-diethylphenylmethyl, 3,5-diethylphenylmethyl, 3,6-diethylphenylmethyl, 2-trifluoromethyl-phenylmethyl, 3-trifluoromethyl-phenylmethyl, 4-trifluoromethyl-phenylmethyl, 2-trifluoromethyl-phenylethyl, 3-trifluoromethyl-phenylethyl, 4-trifluoromethyl-phenylethyl, 2,3-di-trifluoromethyl-phenylmethyl, 2,4-di-trifluoromethyl-phenylmethyl, 2,5-di-trifluoromethyl-phenylmethyl, 2,6-di-trifluoromethyl-phenylmethyl, 3,4-di-trifluoromethyl-phenylmethyl, 3,5-di-trifluoromethyl-phenylmethyl, 3,6-di-trifluoromethyl-phenylmethyl, 2-methoxy-phenylmethyl, 3-methoxy-phenylmethyl, 4-methoxy-phenylmethyl, 2-methoxy-phenylethyl, 3-methoxy-phenylethyl, 4-methoxy-phenylethyl, dimethoxy-phenylmethyl, dimethoxy-phenylethyl, 2,4,6-trimethoxy-phenylmethyl, 2-ethoxy-phenylmethyl, 3-ethoxy-phenylmethyl, 4-ethoxy-phenylmethyl, ethoxy-phenylethyl, diethoxy-phenylmethyl, diethoxy-phenylethyl, 2,4,6-triethoxy-phenylmethyl, 2-fluorophenylmethyl, 3-fluorophenylmethyl, 4-fluorophenylmethyl, 2,3-difluorophenylmethyl, 2,4-difluorophenylmethyl, 2,5-difluorophenylmethyl, 2,6-difluorophenylmethyl, 3,4-difluorophenylmethyl, 3,5-difluorophenylmethyl, 3,6-difluorophenylmethyl, 2-fluorophenylethyl, 3-fluorophenylethyl or 4-fluorophenylethyl, 2-chlorophenylmethyl, 3-chlorophenylmethyl, 4-chlorophenylmethyl, 2,3-

dichlorophenylmethyl, 2,4-dichlorophenylmethyl, 2,5-dichlorophenylmethyl, 2,6-dichlorophenylmethyl, 3,4-dichlorophenylmethyl, 3,5-dichlorophenylmethyl, 3,6-dichlorophenylmethyl, 2-chlorophenylethyl, 3-chlorophenylethyl, 4-chlorophenylethyl, 2-bromophenylmethyl, 3-bromophenylmethyl, 4-bromophenylmethyl, 2,3-dibromophenylmethyl, 2,4-dibromophenylmethyl, 2,5-dibromophenylmethyl, 2,6-dibromophenylmethyl, 3,4-dibromophenylmethyl, 3,5-dibromophenylmethyl, 3,6-dibromophenylmethyl, 2-bromophenylethyl, 3-bromophenylethyl or 4-bromophenylethyl. 2-phenyl-phenylmethyl, 3-phenyl-phenylmethyl, 4-phenyl-phenylmethyl, 2-phenoxy-phenylmethyl, 3-phenoxy-phenylmethyl, 4-phenoxy-phenylmethyl, 2-nitro-phenylmethyl, 3-nitro-phenylmethyl, 4-nitro-phenylmethyl, 2-amino-phenylmethyl, 3-amino-phenylmethyl, 4-amino-phenylmethyl, 2-dimethylamino-phenylmethyl, 3-dimethylamino-phenylmethyl, 4-dimethylamino-phenylmethyl, 2-cyano-phenylmethyl, 3-cyano-phenylmethyl, 4-cyano-phenylmethyl, 2-methanesulfonyl-phenylmethyl, 3-methanesulfonyl-phenylmethyl, 4-methanesulfonyl-phenylmethyl, 2-acid methyl ester-phenylmethyl, 3-acid methyl ester-phenylmethyl or 4-acid methyl ester-phenylmethyl.

The term "substituted C_{1-4}-alkyl" for R^1 is as defined above.

For R^2 and R^3 (independently of each other) the term "substituted C_{1-4}-alkyl" as used herein denotes a C_{1-4}-alkyl group which is substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl, wherein the substituents in substituted aryl and substituted heterocyclyl are 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents, more preferably 1 substituent selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens. Preferably, the term "substituted C_{1-4}-alkyl" as used herein denotes a C_{1-4}-alkyl group substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl, wherein the substituents in substituted aryl and substituted heterocyclyl are 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents, more preferably1 substituent selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are, independently of each other, hydrogen or C_{1-4}-alkyl). The term C_{1-4}-alkyl group as used herein denotes a C_{1-4}-alkyl as defined above, preferably a C_{1-2}-alkyl group, which is substituted with the aforementioned substituents; in case more than one substituent is attached to the C_{1-4}-alkyl group, these substituents can be identical or different from each other. Preferred substituents are aryl, heterocyclyl, substituted aryl or substituted heterocyclyl, more preferably phenyl, pyridyl, substituted phenyl or substituted pyridyl, wherein these substituents are substituted as mentioned above. Examples are 2-

pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 2-pyridylbutyl, methyl-2-pyridyl-methyl, methyl-2-pyridyl-ethyl, dimethyl-2-pyridyl-methyl, ethyl-2-pyridyl-methyl, methoxy-2-pyridyl-methyl, methoxy-2-pyridyl-ethyl, dimethoxy-2-pyridyl-methyl, fluoro-2-pyridyl-methyl, difluoro-2-pyridyl-methyl, chloro-2-pyridyl-methyl, chloro-2-pyridyl-ethyl, dichloro-2-pyridyl-methyl, dichloro-2-pyridyl-methyl, bromo-2-pyridyl-methyl, dibromo-2-pyridyl-methyl, 3-pyridyl-methyl, 3-pyridyl-ethyl, 3-pyridyl-propyl, 3-pyridyl-butyl, methyl-3-pyridyl-methyl, methyl-3-pyridyl-ethyl, dimethyl-3-pyridyl-methyl, ethyl-3-pyridyl-methyl, methoxy-3-pyridyl-methyl, methoxy-3-pyridyl-ethyl, dimethoxy-3-pyridyl-methyl, fluoro-3-pyridyl-methyl, difluoro-3-pyridyl-methyl, chloro-3-pyridyl-methyl, chloro-3-pyridyl-ethyl, dichloro-3-pyridyl-methyl, dichloro-3-pyridyl-methyl, bromo-3-pyridyl-methyl, dibromo-3-pyridyl-methyl, 4-pyridyl-methyl, 4-pyridyl-ethyl, 4-pyridyl-propyl, 4-pyridyl-butyl, methyl-4-pyridyl-methyl, methyl-4-pyridyl-ethyl, dimethyl-4-pyridyl-methyl, ethyl-4-pyridyl-methyl, methoxy-4-pyridyl-methyl, methoxy-4-pyridyl-ethyl, dimethoxy-4-pyridyl-methyl, fluoro-4-pyridyl-methyl, difluoro-4-pyridyl-methyl, chloro-4-pyridyl-methyl, chloro-4-pyridyl-ethyl, dichloro-4-pyridyl-methyl, dichloro-4-pyridyl-methyl, bromo-4-pyridyl-methyl, dibromo-4-pyridyl-methyl, phenylmethyl (benzyl), phenylethyl, phenylpropyl, phenylbutyl, 2-methylphenylmethyl, 3-methylphenylmethyl, 4-methylphenylmethyl, 2-methylphenylethyl, 3-methylphenylethyl, 4-methylphenylethyl, 2,3-dimethylphenylmethyl, 2,4-dimethylphenylmethyl, 2,5-dimethylphenylmethyl, 2,6-dimethylphenylmethyl, 3,4-dimethylphenylmethyl, 3,5-dimethylphenylmethyl, 3,6-dimethylphenylmethyl, 2-ethylphenylmethyl, 3-ethylphenylmethyl, 4-ethylphenylmethyl, 2,3-diethylphenylmethyl, 2,4-diethylphenylmethyl, 2,5-diethylphenylmethyl, 2,6-diethylphenylmethyl, 3,4-diethylphenylmethyl, 3,5-diethylphenylmethyl, 3,6-diethylphenylmethyl, 2-trifluoromethyl-phenylmethyl, 3-trifluoromethyl-phenylmethyl, 4-trifluoromethyl-phenylmethyl, 2-trifluoromethyl-phenylethyl, 2,3-di-trifluoromethyl-phenylmethyl, 2,4-di-trifluoromethyl-phenylmethyl, 2,5-di-trifluoromethyl-phenylmethyl, 2,6-di-trifluoromethyl-phenylmethyl, 3,4-di-trifluoromethyl-phenylmethyl, 3,5-di-trifluoromethyl-phenylmethyl, 3,6-di-trifluoromethyl-phenylmethyl, 2-methoxy-phenylmethyl, 3-methoxy-phenylmethyl, 4-methoxy-phenylmethyl, 2-methoxy-phenylethyl, 3-methoxy-phenylethyl, 4-methoxy-phenylethyl, dimethoxy-phenylmethyl, dimethoxy-phenylethyl, 2,4,6-trimethoxy-phenylmethyl, 2-ethoxy-phenylmethyl, 3-ethoxy-phenylmethyl, 4-ethoxy-phenylmethyl, ethoxy-phenylethyl, diethoxy-phenylmethyl, diethoxy-phenylethyl, 2,4,6-triethoxy-phenylmethyl, 2-fluorophenylmethyl, 3-fluorophenylmethyl, 4-fluorophenylmethyl, 2,3-difluorophenylmethyl, 2,4-difluorophenylmethyl, 2,5-difluorophenylmethyl, 2,6-difluorophenylmethyl, 3,4-difluorophenylmethyl, 3,5-difluorophenylmethyl, 3,6-difluorophenylmethyl, 2-fluorophenylethyl, 3-fluorophenylethyl or 4-fluorophenylethyl, 2-chlorophenylmethyl, 3-chlorophenylmethyl, 4-chlorophenylmethyl, 2,3-dichlorophenylmethyl, 2,4-

dichlorophenylmethyl, 2,5-dichlorophenylmethyl, 2,6-dichlorophenylmethyl, 3,4-dichlorophenylmethyl, 3,5-dichlorophenylmethyl, 3,6-dichlorophenylmethyl, 2-chlorophenylethyl, 3-chlorophenylethyl, 4-chlorophenylethyl, 2-bromophenylmethyl, 3-bromophenylmethyl, 4-bromophenylmethyl, 2,3-dibromophenylmethyl, 2,4-dibromophenylmethyl, 2,5-dibromophenylmethyl, 2,6-dibromophenylmethyl, 3,4-dibromophenylmethyl, 3,5-dibromophenylmethyl, 3,6-dibromophenylmethyl, 2-bromophenylethyl, 3-bromophenylethyl or 4-bromophenylethyl. 2-phenyl-phenylmethyl, 3-phenyl-phenylmethyl, 4-phenyl-phenylmethyl, 2-phenoxy-phenylmethyl, 3-phenoxy-phenylmethyl, 4-phenoxy-phenylmethyl, 2-nitro-phenylmethyl, 3-nitro-phenylmethyl, 4-nitro-phenylmethyl, 2-amino-phenylmethyl, 3-amino-phenylmethyl, 4-amino-phenylmethyl, 2-dimethylamino-phenylmethyl, 3-dimethylamino-phenylmethyl, 4-dimethylamino-phenylmethyl, 2-cyano-phenylmethyl, 3-cyano-phenylmethyl, 4-cyano-phenylmethyl, 2-methanesulfonyl-phenylmethyl, 3-methanesulfonyl-phenylmethyl, 4-methanesulfonyl-phenylmethyl, 2-acid methyl ester-phenylmethyl, 3-acid methyl ester-phenylmethyl or 4-acid methyl ester-phenylmethyl.

The term "substituted C_{1-4}-alkyl" for R^4, R^5 or R^6 are as defined for these substituents R^2 and R^3 (see above).

The term "substituted C_{1-4}-alkyl" for or R and R' (independently of each other) as used herein denotes a C_{1-4}-alkyl group which is substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl, wherein the substituents in substituted aryl and substituted heterocyclyl are 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens (wherein R^7 and R^8 are independently of each other hydrogen or C_{1-4}-alkyl). Preferably, the term "substituted C_{1-4}-alkyl" as used herein denotes a C_{1-4}-alkyl group substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl, wherein the substituents in substituted aryl and substituted heterocyclyl are 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents, more preferably 1 substituent selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R^7 and R^8 are independently of each other hydrogen or C_{1-4}-alkyl). The term C_{1-4}-alkyl group as used herein denotes a C_{1-4}-alkyl as defined above, preferably a C_{1-2}-alkyl group, which is substituted with the aforementioned substituents; in case more

than one substituent is attached to the C_{1-4}-alkyl group, these substituents can be identical or different from each other. Preferred substituents are aryl, heterocyclyl, substituted aryl or substituted heterocyclyl, more preferred substituents are phenyl, pyridyl, substituted phenyl or substituted pyridyl, wherein these substituents are substituted as mentioned above. Examples are cyclopropylmethyl, cyclobutylmethyl, cyclopentylpropyl, cyclohexylbutyl, 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 2-pyridylbutyl, methyl-2-pyridyl-methyl, methyl-2-pyridyl-ethyl, dimethyl-2-pyridyl-methyl, ethyl-2-pyridyl-methyl, methoxy-2-pyridyl-methyl, methoxy-2-pyridyl-ethyl, dimethoxy-2-pyridyl-methyl, fluoro-2-pyridyl-methyl, difluoro-2-pyridyl-methyl, chloro-2-pyridyl-methyl, chloro-2-pyridyl-ethyl, dichloro-2-pyridyl-methyl, dichloro-2-pyridyl-methyl, bromo-2-pyridyl-methyl, dibromo-2-pyridyl-methyl, 3-pyridyl-methyl, 3-pyridyl-ethyl, 3-pyridyl-propyl, 3-pyridyl-butyl, methyl-3-pyridyl-methyl, methyl-3-pyridyl-ethyl, dimethyl-3-pyridyl-methyl, ethyl-3-pyridyl-methyl, methoxy-3-pyridyl-methyl, methoxy-3-pyridyl-ethyl, dimethoxy-3-pyridyl-methyl, fluoro-3-pyridyl-methyl, difluoro-3-pyridyl-methyl, chloro-3-pyridyl-methyl, chloro-3-pyridyl-ethyl, dichloro-3-pyridyl-methyl, dichloro-3-pyridyl-methyl, bromo-3-pyridyl-methyl, dibromo-3-pyridyl-methyl, 4-pyridyl-methyl, 4-pyridyl-ethyl, 4-pyridyl-propyl, 4-pyridyl-butyl, methyl-4-pyridyl-methyl, methyl-4-pyridyl-ethyl, dimethyl-4-pyridyl-methyl, ethyl-4-pyridyl-methyl, methoxy-4-pyridyl-methyl, methoxy-4-pyridyl-ethyl, dimethoxy-4-pyridyl-methyl, fluoro-4-pyridyl-methyl, difluoro-4-pyridyl-methyl, chloro-4-pyridyl-methyl, chloro-4-pyridyl-ethyl, dichloro-4-pyridyl-methyl, dichloro-4-pyridyl-methyl, bromo-4-pyridyl-methyl, dibromo-4-pyridyl-methyl, phenylmethyl (benzyl), phenylethyl, phenylpropyl, phenylbutyl, 2-methylphenylmethyl, 3-methylphenylmethyl, 4-methylphenylmethyl, 2-methylphenylethyl, 3-methylphenylethyl, 4-methylphenylethyl, 2,3-dimethylphenylmethyl, 2,4-dimethylphenylmethyl, 2,5-dimethylphenylmethyl, 2,6-dimethylphenylmethyl, 3,4-dimethylphenylmethyl, 3,5-dimethylphenylmethyl, 3,6-dimethylphenylmethyl, 2-ethylphenylmethyl, 3-ethylphenylmethyl, 4-ethylphenylmethyl, 2,3-diethylphenylmethyl, 2,4-diethylphenylmethyl, 2,5-diethylphenylmethyl, 2,6-diethylphenylmethyl, 3,4-diethylphenylmethyl, 3,5-diethylphenylmethyl, 3,6-diethylphenylmethyl, 2-trifluoromethyl-phenylmethyl, 3-trifluoromethyl-phenylmethyl, 4-trifluoromethyl-phenylmethyl, 2-trifluoromethyl-phenylethyl, 2,3-di-trifluoromethyl-phenylmethyl, 2,4-di-trifluoromethyl-phenylmethyl, 2,5-di-trifluoromethyl-phenylmethyl, 2,6-di-trifluoromethyl-phenylmethyl, 3,4-di-trifluoromethyl-phenylmethyl, 3,5-di-trifluoromethyl-phenylmethyl, 3,6-di-trifluoromethyl-phenylmethyl, 2-methoxy-phenylmethyl, 3-methoxy-phenylmethyl, 4-methoxy-phenylmethyl, 2-methoxy-phenylethyl, 3-methoxy-phenylethyl, 4-methoxy-phenylethyl, dimethoxy-phenylmethyl, dimethoxy-phenylethyl, 2,4,6-trimethoxy-phenylmethyl, 2-ethoxy-phenylmethyl, 3-ethoxy-phenylmethyl, 4-ethoxy-phenylmethyl, ethoxy-phenylethyl, diethoxy-phenylmethyl, diethoxy-phenylethyl, 2,4,6-triethoxy-phenylmethyl, 2-fluorophenylmethyl,

3-fluorophenylmethyl, 4-fluorophenylmethyl, 2,3-difluorophenylmethyl, 2,4-difluorophenylmethyl, 2,5-difluorophenylmethyl, 2,6-difluorophenylmethyl, 3,4-difluorophenylmethyl, 3,5-difluorophenylmethyl, 3,6-difluorophenylmethyl, 2-fluorophenylethyl, 3-fluorophenylethyl or 4-fluorophenylethyl, 2-chlorophenylmethyl, 3-chlorophenylmethyl, 4-chlorophenylmethyl, 2,3-dichlorophenylmethyl, 2,4-dichlorophenylmethyl, 2,5-dichlorophenylmethyl, 2,6-dichlorophenylmethyl, 3,4-dichlorophenylmethyl, 3,5-dichlorophenylmethyl, 3,6-dichlorophenylmethyl, 2-chlorophenylethyl, 3-chlorophenylethyl, 4-chlorophenylethyl, 2-bromophenylmethyl, 3-bromophenylmethyl, 4-bromophenylmethyl, 2,3-dibromophenylmethyl, 2,4-dibromophenylmethyl, 2,5-dibromophenylmethyl, 2,6-dibromophenylmethyl, 3,4-dibromophenylmethyl, 3,5-dibromophenylmethyl, 3,6-dibromophenylmethyl, 2-bromophenylethyl, 3-bromophenylethyl or 4-bromophenylethyl. 2-phenyl-phenylmethyl, 3-phenyl-phenylmethyl, 4-phenyl-phenylmethyl, 2-phenoxy-phenylmethyl, 3-phenoxy-phenylmethyl, 4-phenoxy-phenylmethyl, 2-nitro-phenylmethyl, 3-nitro-phenylmethyl, 4-nitro-phenylmethyl, 2-amino-phenylmethyl, 3-amino-phenylmethyl, 4-amino-phenylmethyl, 2-dimethylamino-phenylmethyl, 3-dimethylamino-phenylmethyl, 4-dimethylamino-phenylmethyl, 2-cyano-phenylmethyl, 3-cyano-phenylmethyl, 4-cyano-phenylmethyl, 2-methanesulfonyl-phenylmethyl, 3-methanesulfonyl-phenylmethyl, 4-methanesulfonyl-phenylmethyl, 2-acid methyl ester-phenylmethyl, 3-acid methyl ester-phenylmethyl or 4-acid methyl ester-phenylmethyl.

The term "alkoxy" as used herein, and if not specified by the number of carbon atoms, denotes a straight or branched chain alkyl-oxy group wherein the "alkyl" portion is as defined above such as methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, tert.-butyloxy, pentyloxy, hexyloxy, heptyloxy including their different isomers. More preferred alkoxy groups within the invention are methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy or tert.-butyloxy.

The terms " COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R " within the invention, R and R' are, independently of each other, hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl, wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and wherein substituted aryl are substituted with 1-5 substituents and substituted heterocyclyl are substituted with 1-4 substituents, these substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl and C_{1-4}-alkyl

substituted with 1-3 halogens (R^7 and R^8 are independently of each other hydrogen or C_{1-4}-alkyl). Preferably, R and/or R' are independently of each other hydrogen, C_{1-12}-alkyl or aryl, more preferable hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl or phenyl. Examples for the terms " COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R " are SO_2H, SO_2CH_3, $SO_2C_2H_5$, carboxylic acid methyl ester, carboxylic acid ethyl ester, amino, methylamino, dimethylamino or phenylamino.

The term "aryl" as used herein denotes a phenyl and naphthyl, both optionally benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle e.g. to cyclohexyl or cyclopentyl.

Aryl in R^1 is as defined above and is, most preferably phenyl.

Aryl in R^2 and R^3 are, independently of each other, as defined above and are most preferably phenyl.

Aryl in R^4, R^5 or R and R' (independently of each other) are as defined above, most preferably phenyl.

The term "aryl-C(=O)-," as used herein for R^4 or R^5 denotes an aryl group as defined above (e.g. phenyl and naphthyl) attached to a keto function -C(=O)-. Preferred example is benzoyl.

The term "aryl-CH(OH)-" as used herein for R^4 or R^5 denotes an aryl group such as a phenyl or naphthyl group, preferably a phenyl group, attached to a hydroxy-methyl group. Preferred aryl-CH(OH)- is phenyl-CH(OH)-.

The term "substituted aryl" as used herein denotes substituted phenyl and naphthyl, both optionally benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle e.g. to cyclohexyl or cyclopentyl. Suitable substituents for aryl can be selected from 1, 2, 3, 4 or 5 substituents, or 1, 2, 3 or 4 substituent, preferably 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent, wherein these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens; in case more than one substituent is attached to the aryl group, these substituents can be identical or different from each other. Preferred substituents for aryl are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are independently of each other as defined below). More preferably, substituents for aryl are selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens. Examples of substituted

aryl groups are 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 3,6-dimethylphenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl, 2,5-dimethoxy-phenyl, 2,6-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethoxy-phenyl, 3,6-dimethoxy-phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3,6-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,6-dichlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 3,6-dibromophenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 2,3-di-trifluoromethyl-phenyl, 2,4-di-trifluoromethyl-phenyl, 2,5-di-trifluoromethyl-phenyl, 2,6-di-trifluoromethyl-phenyl, 3,4-di-trifluoromethyl-phenyl, 3,5-di-trifluoromethyl-phenyl, 3,6-di-trifluoromethyl-phenyl, 2-amino-phenyl, 3-amino-phenyl, 4-amino-phenyl, 2,3-di-amino-phenyl, 2,4-di-amino-phenyl, 2,5-di-amino-phenyl, 2,6-di-amino-phenyl, 3,4-di-amino-phenyl, 3,5-di-amino-phenyl, 3,6-di-amino-phenyl, 2-dimethylamino-phenyl, 3-dimethylamino-phenyl, 4-dimethylamino-phenyl, 2,3-di-dimethylamino-phenyl, 2,4-di-dimethylamino-phenyl, 2,5-di-dimethylamino-phenyl, 2,6-di-dimethylamino-phenyl, 3,4-di-dimethylamino-phenyl, 3,5-di-dimethylamino-phenyl, 3,6-di-dimethylamino-phenyl, 2-nitro-phenyl, 3-nitro-phenyl, 4-nitro-phenyl, 2,3-di-nitro-phenyl, 2,4-di-nitro-phenyl, 2,5-di-nitro-phenyl, 2,6-di-nitro-phenyl, 3,4-di-nitro-phenyl, 3,5-di-nitro-phenyl, 3,6-di-nitro-phenyl, 2-cyano-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 2,3-di-cyano-phenyl, 2,4-di-cyano-phenyl, 2,5-di-cyano-phenyl, 2,6-di-cyano-phenyl, 3,4-di-cyano-phenyl, 3,5-di-cyano-phenyl, 3,6-di-cyano-phenyl, 2-carboxylic acid-phenyl, 3-carboxylic acid-phenyl, 4-carboxylic acid-phenyl, 2,3-di-carboxylic acid-phenyl, 2,4-di-carboxylic acid-phenyl, 2,5-di-carboxylic acid-phenyl, 2,6-di-carboxylic acid-phenyl, 3,4-di-carboxylic acid-phenyl, 3,5-di-carboxylic acid-phenyl, 3,6-di-carboxylic acid-phenyl, 2-carboxylic acid methyl ester-phenyl, 3-carboxylic acid methyl ester-phenyl, 4-carboxylic acid methyl ester-phenyl, 2,3-di-carboxylic acid methyl ester-phenyl, 2,4-di-carboxylic acid methyl ester-phenyl, 2,5-di-carboxylic acid methyl ester-phenyl, 2,6-di-carboxylic acid methyl ester-phenyl, 3,4-di-carboxylic acid methyl ester-phenyl, 3,5-di-carboxylic acid methyl ester-phenyl or 3,6-di-carboxylic acid methyl ester-phenyl.

Substituted aryl for R^1, R^2 and R^3 (independently of each other), R^4, R^5, R and R' (independently of each other) are as defined above.

The term "substituted aryl-C(=O)-" as used herein for R^4 or R^5 denotes a substituted aryl group as defined above, attached to a keto function -C(=O)-. Suitable substituents for substituted aryl-C(=O)- can be selected from 1, 2, 3, 4 or 5 substituents, or 1, 2, 3 or 4 substituent, preferably 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent, wherein these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens; in case more than one substituent is attached to the aryl group, these substituents can be identical or different from each other. Preferred substituents for aryl are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are independently of each other as defined below). More preferably, substituents for substituted aryl-C(=O)-are selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens.

The term "substituted aryl-CH(OH)-" as used herein for R^4 or R^5 denotes a substituted phenyl group or a substituted naphthyl group, preferably a substituted phenyl group, attached to a hydroxy-methyl group. Suitable substituents for substituted aryl-CH(OH)-can be selected from 1, 2, 3, 4 or 5 substituents, or 1, 2, 3 or 4 substituent, preferably 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent, wherein these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens; in case more than one substituent is attached to the aryl group, these substituents can be identical or different from each other. Preferred substituents for aryl are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are independently of each other as defined below). More preferably, substituents for substituted aryl-CH(OH)-are selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens. Examples are the aforementioned substituted aryl groups attached to a hydroxy-methyl group, such as 2-methyl-phenyl-hydroxymethyl, 3-methyl-phenyl-hydroxymethyl, 4-methyl-phenyl-hydroxymethyl, 2,3-dimethylphenyl-hydroxymethyl, 2,4-dimethylphenyl-hydroxymethyl, 2,5-dimethylphenyl-hydroxymethyl, 2,6-dimethylphenyl-hydroxymethyl, 3,4-dimethylphenyl-hydroxymethyl, 3,5-dimethylphenyl-hydroxymethyl, 3,6-dimethylphenyl-hydroxymethyl, 2-methoxy-phenyl-hydroxymethyl, 3-methoxy-phenyl-hydroxymethyl, 4-methoxy-phenyl-hydroxymethyl, 2,3-dimethoxy-phenyl-hydroxymethyl, 2,4-dimethoxy-phenyl-hydroxymethyl, 2,5-dimethoxy-phenyl-hydroxymethyl, 2,6-dimethoxy-phenyl-hydroxymethyl, 3,4-dimethoxy-phenyl-hydroxymethyl, 3,5-dimethoxy-phenyl-hydroxymethyl, 3,6-dimethoxy-phenyl-hydroxymethyl.

The term "heterocyclyl" as used herein denotes an aromatic or non-aromatic monocyclic or bicyclic heterocyclic system which contains 1, 2, 3 or 4 hetero atoms, preferably 1, 2 or 3 hetero atoms, with the hetero atoms being selected from nitrogen, oxygen and sulfur. Examples of heterocyclyl are 2-furyl, 3-furyl, 1-pyrrolyl, 2-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-indolyl, 2-indolyl or 3-indolyl, pyridazin-3-yl, pyridazin-4-yl, thiophen-2-yl, thiophen-3-yl, [1,3,4]thiadiazol-2-yl, [1,3,4]thiadiazol-5-yl, or tetrahydro-pyran-4-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl or pyrrolidin-5-yl.

Heterocyclyl for R^1 is as defined above and is, preferably, 2-pyridyl, 3-pyridyl or 4-pyridyl.

Heterocyclyl for R^2 and R^3 (independently of each other), R^4, R^5 or R and R' (independently of each other) are as defined above. Examples are 2-furyl, 3-furyl, 1-pyrrolyl, 2-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-indolyl, 2-indolyl or 3-indolyl, pyridazin-3-yl, pyridazin-4-yl, thiophen-2-yl, thiophen-3-yl, [1,3,4]thiadiazol-2-yl or tetrahydro-pyran-4-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl or pyrrolidin-5-yl.

The term "heterocyclyl-C(=O)-," as used herein for R^4 or R^5 denotes a heterocyclyl group such as defined above (e.g. 2-furyl, 3-furyl, 1-pyrrolyl, 2-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-indolyl, 2-indolyl or 3-indolyl, pyridazin-3-yl, pyridazin-4-yl, thiophen-2-yl, thiophen-3-yl, [1,3,4]thiadiazol-2-yl, [1,3,4]thiadiazol-5-yl, or tetrahydro-pyran-4-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl or pyrrolidin-5-yl) attached to a keto function -C(=O)-.

The term "heterocyclyl-CH(OH)-" as used herein for R^4 and R^5 denotes a heterocyclyl group such as defined above (e.g. 2-furyl, 3-furyl, 1-pyrrolyl, 2-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-indolyl, 2-indolyl or 3-indolyl, pyridazin-3-yl, pyridazin-4-yl, thiophen-2-yl, thiophen-3-yl, [1,3,4]thiadiazol-2-yl, [1,3,4]thiadiazol-5-yl, or tetrahydro-pyran-4-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl or pyrrolidin-5-yl) attached to a hydroxy-methyl group.

The term "substituted heterocyclyl" as used herein denotes substituted aromatic or non-aromatic monocyclic or bicyclic heterocyclic systems which contain one or more hetero atoms selected from nitrogen, oxygen and sulfur, such as 2-furyl, 3-furyl, 1-

pyrrolyl, 2-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-indolyl, 2-indolyl or 3-indolyl, [1,3,4]thiadiazol-2-yl, [1,3,4]thiadiazol-5-yl, or piperidin-4-yl, pyridazin-3-yl, pyridazin-4-yl, thiophen-2-yl, thiophen-3-yl, tetrahydro-pyran-4yl, piperidin-4-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl, pyrrolidin-5-yl. Suitable substituents for heterocyclyl can be selected from 1, 2, 3 or 4 substituents, preferably 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent, wherein these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are as defined below); in case more than one substituent is attached to the heterocyclyl group, these substituents can be identical or different from each other. Preferred substituents for heterocyclyl are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens. More preferable substituents for heterocyclyl are selected from C_{1-4}-alkoxy, COR, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens, more preferred substituents for heterocyclyl are selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens. Examples of substituted heterocyclyl groups are 2-methyl-pyridyl, 3-methyl-pyridyl, 4-methyl-pyridyl, 2,3-dimethylpyridyl, 2,4-dimethylpyridyl, 2,5-dimethylpyridyl, 2,6-dimethylpyridyl, 3,4-dimethylpyridyl, 3,5-dimethylpyridyl, 3,6-dimethylpyridyl, 2-methoxy-pyridyl, 3-methoxy-pyridyl, 4-methoxy-pyridyl, 2,3-dimethoxy-pyridyl, 2,4-dimethoxy-pyridyl, 2,5-dimethoxy-pyridyl, 2,6-dimethoxy-pyridyl, 3,4-dimethoxy-pyridyl, 3,5-dimethoxy-pyridyl, 3,6-dimethoxy-pyridyl, 2-fluoro-pyridyl, 3-fluoro-pyridyl, 4-fluoro-pyridyl, 2,3-difluoro-pyridyl, 2,4-difluoro-pyridyl, 2,5-difluoro-pyridyl, 2,6-difluoro-pyridyl, 3,4-difluoro-pyridyl, 3,5-difluoro-pyridyl, 3,6-difluoro-pyridyl, 2-chloro-pyridyl, 3-chloro-pyridyl, 4-chloro-pyridyl, 2,3-dichloro-pyridyl, 2,4-dichloro-pyridyl, 2,5-dichloro-pyridyl, 2,6-dichloro-pyridyl, 3,4-dichloro-pyridyl, 3,5-dichloro-pyridyl, 3,6-dichloro-pyridyl, 2-bromo-pyridyl, 3-bromo-pyridyl, 4-bromo-pyridyl, 2,3-dibromo-pyridyl, 2,4-dibromo-pyridyl, 2,5-dibromo-pyridyl, 2,6-dibromo-pyridyl, 3,4-dibromo-pyridyl, 3,5-dibromo-pyridyl, 3,6-dibromo-pyridyl, 2-trifluoromethyl-pyridyl, 3-trifluoromethyl-pyridyl, 4-trifluoromethyl-pyridyl, 2,3-di-trifluoromethyl-pyridyl, 2,4-di-trifluoromethyl-pyridyl, 2,5-di-trifluoromethyl-pyridyl, 2,6-di-trifluoromethyl-pyridyl, 3,4-di-trifluoromethyl-pyridyl, 3,5-di-trifluoromethyl-pyridyl, 3,6-di-trifluoromethyl-pyridyl, 5-methyl-[1,3,4]thiadiazol-2-yl, 2-methyl-[1,3,4]thiadiazol-5-yl, 5-ethyl-[1,3,4]thiadiazol-2-yl, 2-ethyl-[1,3,4]thiadiazol-5-yl, 1-formyl-piperidin-4-yl, 2-formyl-piperidin-4-yl or 3-formyl-piperidin-4-yl. For all the cited examples for "heterocyclyl" these substituents can be at any chemically possible position. For example methylpyridyl means that the methyl substituent may be attached in the 3, 4, 5 or 6 position of a 2-pyridyl or in the 2, 4, 5 or 6 position of a 3-pyridyl or in the 2, 3, 5 or 6 position of a 4-pyridyl.

Substituted heterocyclyl in R^1 is as defined above, preferably 2-pyridyl, 3-pyridyl or 4-pyridyl, substituted with these substituents as defined above.

Substituted heterocyclyl for R^2 and R^3 (independently of each other), R and R' (independently of each other), R^4 and R^5 are as defined above.

The term "substituted heterocyclyl-CH(OH)-" as used herein for R^4 or R^5 denotes a substituted heterocyclyl group such as defined above attached to a hydroxy-methyl group. Suitable substituents for substituted heterocyclyl-CH(OH)-can be selected from 1, 2, 3 or 4 substituents, preferably 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent, wherein these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens; in case more than one substituent is attached to the heterocyclyl group, these substituents can be identical or different from each other. Preferred substituents for heterocyclyl are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are independently of each other as defined below). More preferably, substituents for substituted heterocyclyl -C(=O)-are selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens.

The term "substituted heterocyclyl-C(=O)-" as used herein for R^4 or R^5 denotes a substituted heterocyclyl group such as defined above attached to a keto function -C(=O)-. Suitable substituents for substituted heterocyclyl-C(=O)- can be selected from 1, 2, 3 or 4 substituents, preferably 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and most preferably 1 substituent, wherein these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens; in case more than one substituent is attached to the heterocyclyl group, these substituents can be identical or different from each other. Preferred substituents for heterocyclyl are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens (wherein R and R' are independently of each other as defined below). More preferably, substituents for substituted heterocyclyl-C(=O)- are selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens.

The term halogen stands for fluorine, chlorine, bromine and iodine.

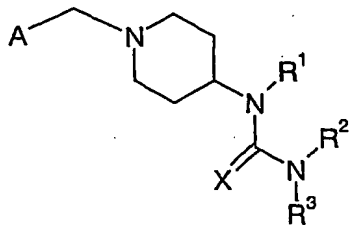
The term "X" represents S and O, preferably O.

The compounds of the instant invention may contain an olefinic double bond, this can have the (E) or (Z) configuration. All such isomeric forms of these compounds are embraced by the present invention. The independent syntheses of these compounds or their chromatograpic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein.

Any functional (i.e. reactive) group present in any of the compounds of the invention may be protected with a protecting group which is known *per se*, for example, as described in "Protective Groups in Organic Synthesis", 2nd Ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. Groups which are to be protected are for example "hydroxy groups", "carboxylic acid groups" "amino groups" and "ketone groups". The term "hydroxy protecting group" includes protecting groups which are usually used to replace the proton of the hydroxy group. The term "carboxylic acid protecting group" includes protecting groups which are usually used to replace the proton of the carboxyl group. The term "amino protecting group" as used herein includes protecting groups that are usually used to replace one proton or both protons of the amino group. Such groups are often employed in peptide chemistry. The term "ketone protecting group" includes protecting groups known in the art such as ketals or thioketals.

Compounds of formula I which are acidic can form pharmaceutically acceptable salts with bases such as alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide, barium hydroxide and magnesium hydroxide), and with organic bases (e.g. N-ethyl piperidine, dibenzylamine, and the like). Those compounds of formula (I) which are basic can form pharmaceutically acceptable salts with inorganic acids such as hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid, nitric acid and phosphoric acid, and the like, and with organic acids (e.g. with acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid and p-toluene sulphonic acid, and the like). The formation and isolation of such salts can be carried out according to methods known in the art.

A preferred embodiment of the invention are novel compounds of formula I



I

wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

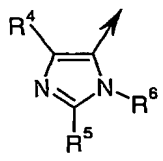
wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4

substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

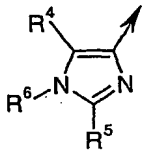
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, CN, COR, CO_2R, CONRR', NHCOR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl, substituted aryl-C(=O)- or substituted aryl-CH(OH)- are substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted heterocyclyl, substituted heterocyclyl-C(=O)- or substituted heterocyclyl-CH(OH)- are substituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, halogen, COR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl, substituted aryl-C(=O)- or substituted aryl-CH(OH)- are substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted heterocyclyl, substituted heterocyclyl-C(=O)- or substituted heterocyclyl-CH(OH)- are substituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^6 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{3-8}-cycloalkyl, COR, CO_2R, CONRR', NHCOR, SO_2NRR', SO_2R,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens;

R and R' are independently of each other hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl are substituted with 1-5 substituents and substituted heterocyclyl are substituted with 1-4 substituents, these substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^7 and R^8 are independently of each other hydrogen or C_{1-4}-alkyl;

as well as ethers or hydrolyzable esters of compounds of formula I and pharmaceutically acceptable salts thereof.

Other preferred embodiments of the invention are novel compounds of formula I wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl or heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

preferably wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl, substituted phenyl and substituted pyridyl; wherein substituted phenyl and substituted pyridyl are substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

more preferably wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, CO_2R, NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

most preferably wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, phenyl, phenoxy, chlorine, CN, NO_2, CO_2R, NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 fluorines, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, chlorine, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 fluorines;

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

preferably wherein

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl, substituted phenyl and substituted pyridyl, wherein substituted phenyl or substituted pyridyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

more preferably wherein

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl, wherein substituted phenyl is substituted with C_{1-4}-alkoxy, halogen, NO_2, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, CO_2R, NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

most preferably wherein

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with NO_2, and

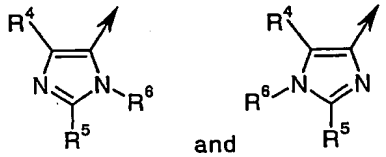
wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, fluorine, chlorine, CN, NO_2, CO_2R, NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 fluorines;

X is S or O,

preferably wherein

X is O;

A is selected from the group consisting of:



A1 A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, CO_2R or aryl,

preferably wherein

R^4 is hydrogen, C_{1-12}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, aryl, substituted aryl, aryl-C(=O)-, aryl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

preferably wherein

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, heterocyclyl, substituted phenyl and substituted heterocyclyl; wherein substituted phenyl and substituted heterocyclyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

more preferably wherein

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens,

most preferably wherein

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, chlorine, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 fluorines;

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens,

preferably wherein

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, heterocyclyl, substituted phenyl and substituted heterocyclyl; wherein substituted phenyl or substituted heterocyclyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens,

more preferably wherein

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens,

most preferably wherein

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl;

R and R' are independently of each other hydrogen or C_{1-12}-alkyl.

Other preferred embodiments of the invention are novel compounds of formula I wherein

R^1 is hydrogen, C_{1-7}-alkyl, C_{3-6}-cycloalkyl, allyl, substituted C_{1-2}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-6}-cycloalkyl, phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-2}-alkoxy, phenyl, phenoxy, chlorine, CN, NO_2, CO_2R, NRR', SO_2R, C_{1-2}-alkyl or C_{1-2}-alkyl substituted with 1-3 fluorines, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-2}-alkoxy, chlorine, C_{1-2}-alkyl and C_{1-2}-alkyl substituted with 1-3 fluorines,

preferably wherein

R^1 is hydrogen, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, allyl, substituted C_1-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-6}-cycloalkyl, phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with C_1-alkoxy, phenyl, phenoxy, chlorine, CN, NO_2, CO_2R, NRR', SO_2R, C_1-alkyl or C_1-alkyl substituted with 1-3 fluorines, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_1-alkoxy, chlorine, C_1-alkyl and C_1-alkyl substituted with 1-3 fluorines;

R^2 and R^3 are independently of each other hydrogen, C_{1-7}-alkyl, C_{3-6}-cycloalkyl, substituted C_{1-2}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with NO_2, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-2}-alkoxy, fluorine, chlorine, CN, NO_2, CO_2R, NRR', C_{1-2}-alkyl and C_{1-2}-alkyl substituted with 1-3 fluorines,

preferably wherein

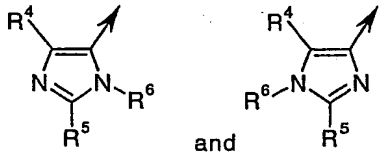
R^2 and R^3 are independently of each other hydrogen, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, substituted C_1-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with NO_2, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_1-alkoxy, fluorine, chlorine, CN, NO_2, CO_2R, NRR', C_1-alkyl and C_1-alkyl substituted with 1-3 fluorines;

X is S or O;

A is selected from the group consisting of:



A1 and A2

wherein

R^4 is hydrogen, C_{1-7}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-7}-alkyl, substituted C_{1-2}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-2}-alkoxy, chlorine, C_{1-2}-alkyl and C_{1-2}-alkyl substituted with 1-3 fluorines,

preferably wherein

R^5 is hydrogen, C_{1-4}-alkyl, substituted C_1-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_1-alkoxy, chlorine, C_1-alkyl and C_1-alkyl substituted with 1-3 fluorines;

R^6 is hydrogen, C_{1-7}-alkyl or substituted C_{1-2}-alkyl,

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl,

preferably wherein

R^6 is hydrogen, C_{1-5}-alkyl or substituted C_1-alkyl,

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from phenyl;

R and R' are independently of each other hydrogen or C_{1-7}-alkyl,

preferably wherein

R and R' are independently of each other hydrogen or C_{1-4}-alkyl.

Another preferred embodiment of the invention are novel compounds of formula I wherein

X is O, or

wherein

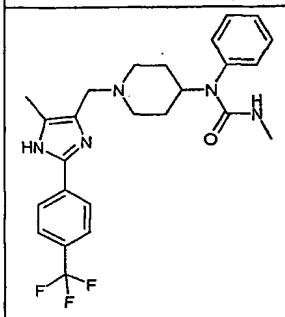
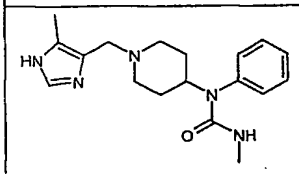
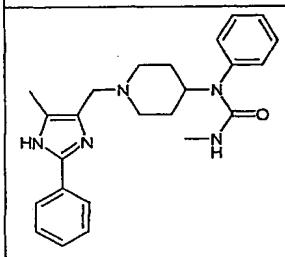
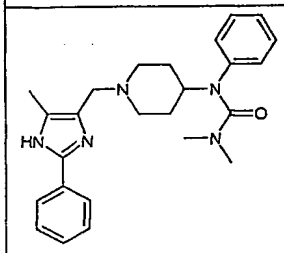
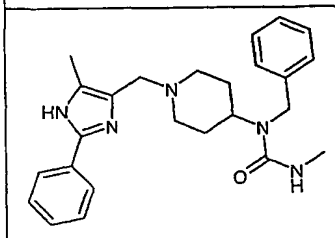
A is A1, or

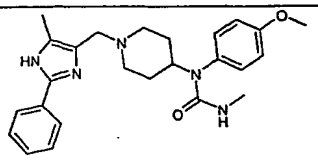
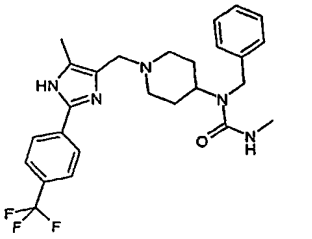
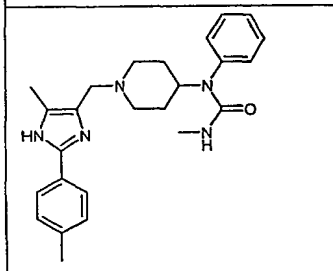
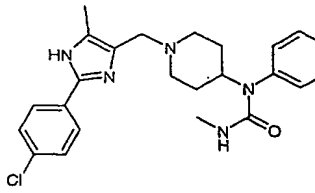
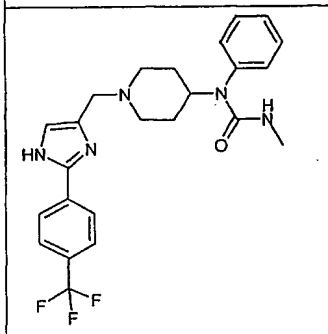
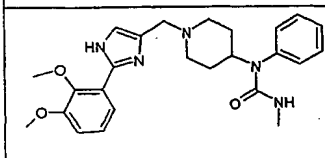
wherein

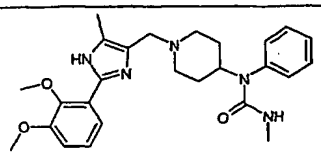
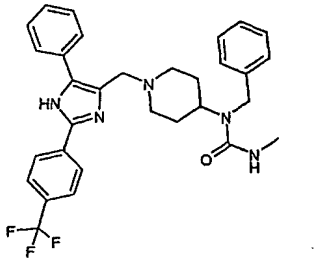
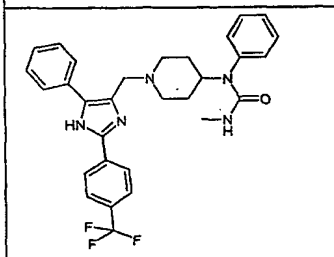
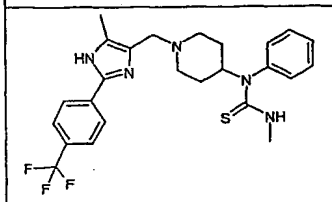
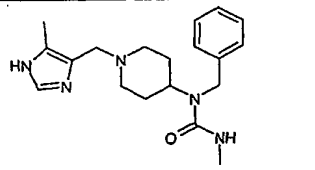
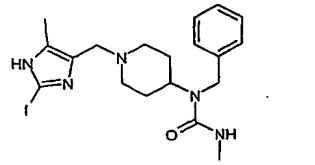
A is A2.

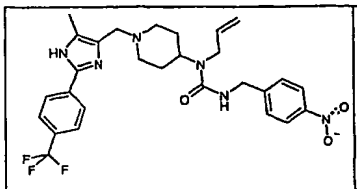
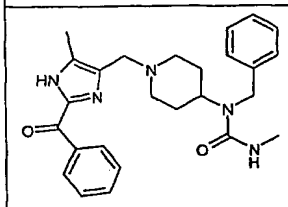
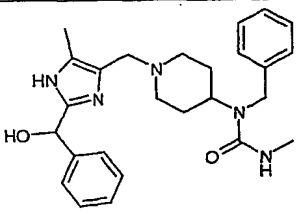
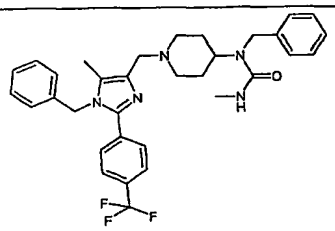
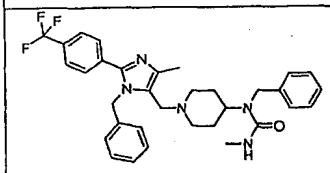
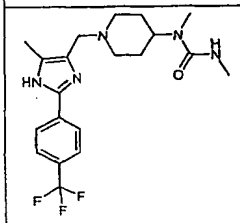
More preferred embodiments of compounds of formula I, as well as ethers or hydrolyzable esters of compounds of formula I and pharmaceutically acceptable salts thereof, are listed in table 1:

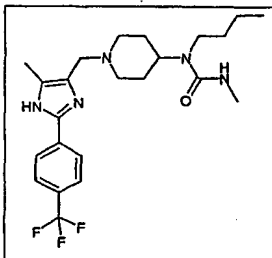
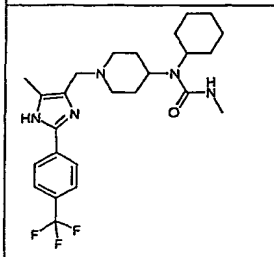
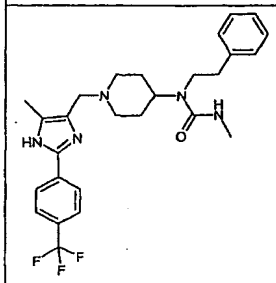
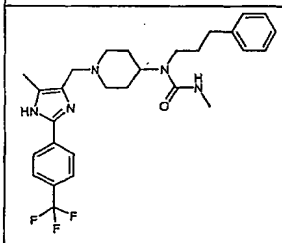
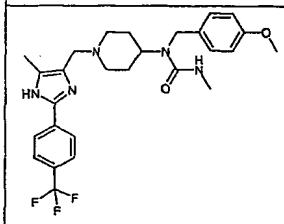
Table 1

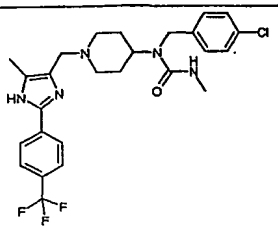
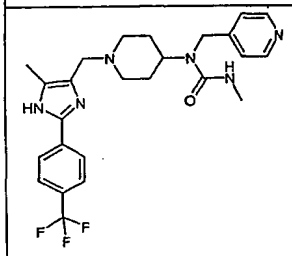
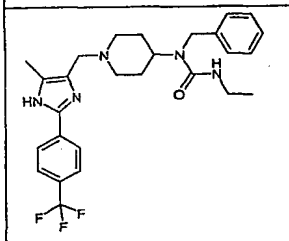
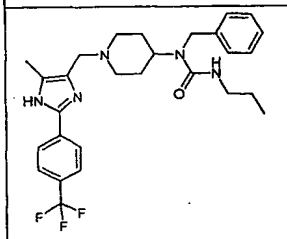
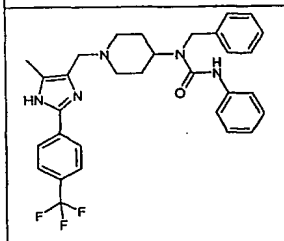
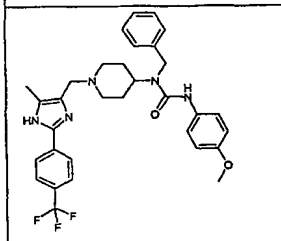
STRUCTURE	SYSTEMATIC NAME
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea
	3-Methyl-1-[1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-phenylurea
	3-Methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-phenylurea
	1,1-Dimethyl-3-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-3-phenylurea
	1-Benzyl-3-methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea

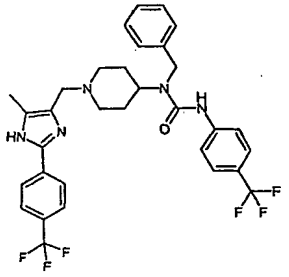
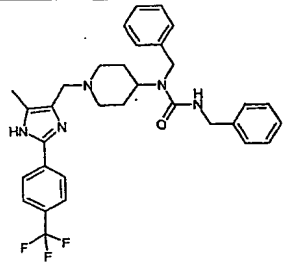
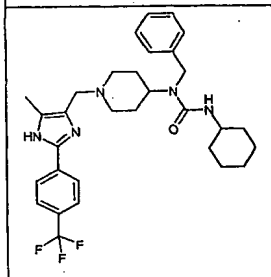
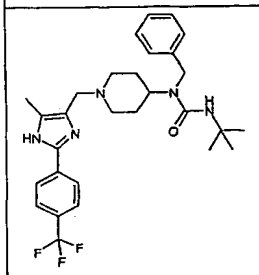
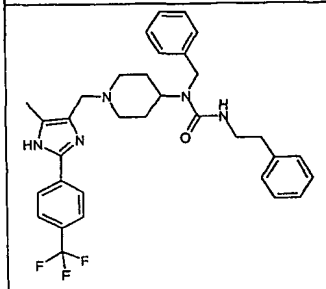
	1-(4-Methoxyphenyl)-3-methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea
	1-Benzyl-3-methyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	3-Methyl-1-[1-[[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylurea
	1-[1-[[2-(4-Chlorophenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea
	3-Methyl-1-phenyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-[1-[[2-(2,3-Dimethoxyphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea

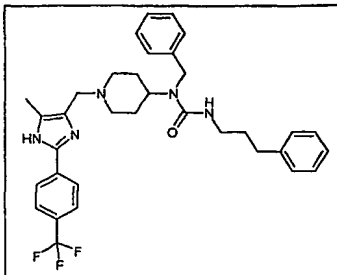
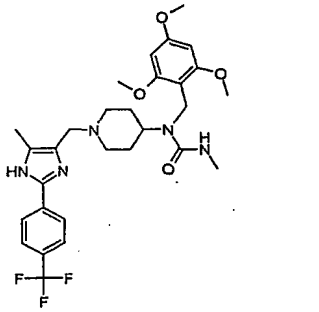
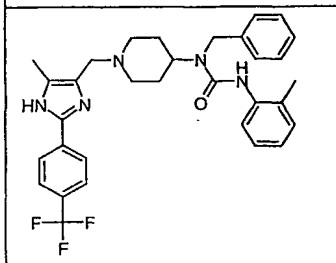
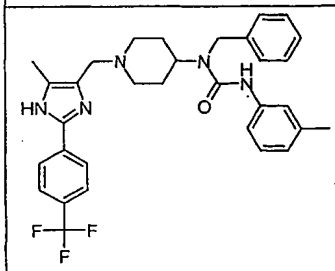
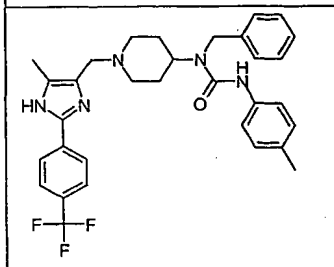
	1-[1-[[2-(2,3-Dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea
	1-Benzyl-3-methyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	3-Methyl-1-phenyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	3-Methyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylthiourea
	1-Benzyl-3-methyl-1-[1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea
	1-Benzyl-1-[1-[(2-iodo-5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-3-methylurea

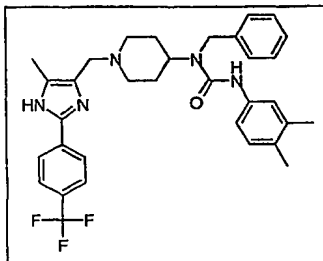
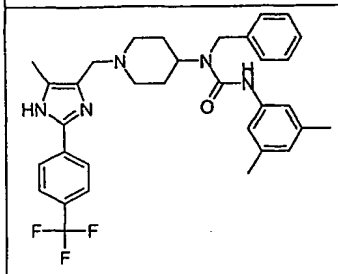
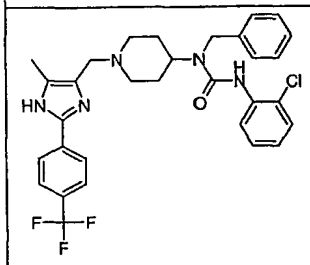
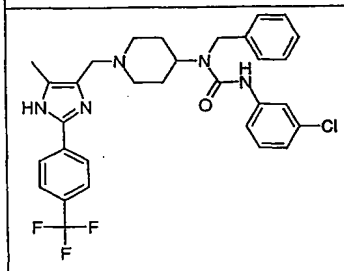
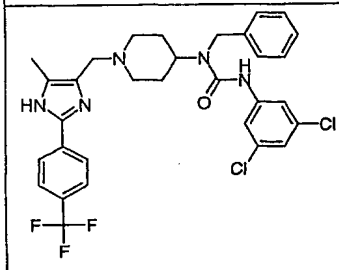
	1-Allyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-nitrobenzyl)urea
	1-[1-[(2-Benzoyl-5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-benzyl-3-methylurea
	1-Benzyl-1-[1-[[2-[(RS)-(hydroxy)(phenyl)methyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea
	1-Benzyl-1-[1-[[1-benzyl-5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea
	1-Benzyl-1-[1-[[3-benzyl-5-methyl-2-[4-(trifluoromethyl)phenyl]-3H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1,3-dimethylurea

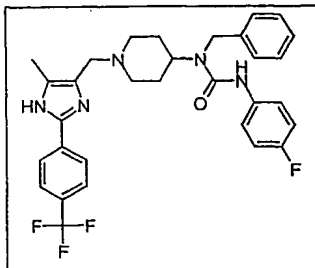
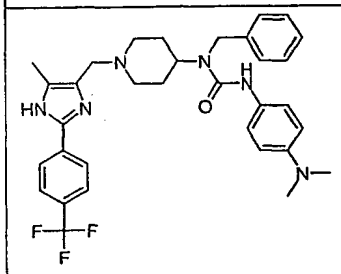
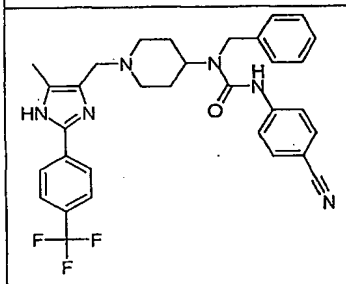
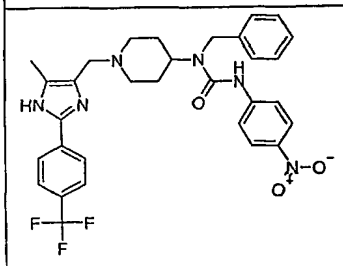
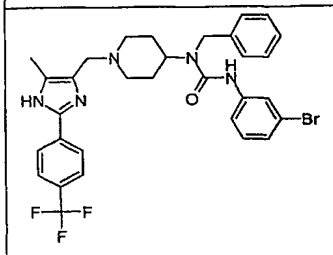
	1-Butyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea
	1-Cyclohexyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-(2-phenethyl)urea
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-(3-phenylpropyl)urea
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-(4-methoxybenzyl)-3-methylurea

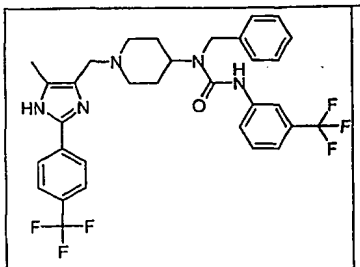
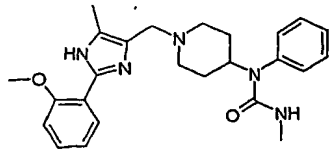
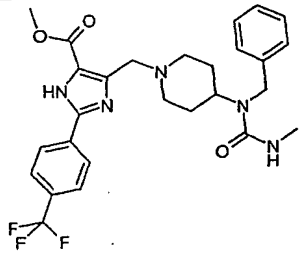
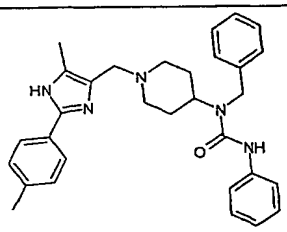
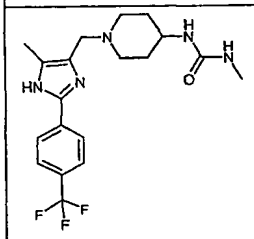
	1-(4-Chlorobenzyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-[(4-pyridyl)methyl]urea
	1-Benzyl-3-ethyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-propylurea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-phenylurea
	1-Benzyl-1-[1-[[2-[4-trifluoromethyl-phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-methoxyphenyl)urea

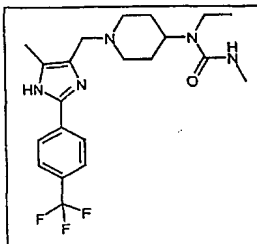
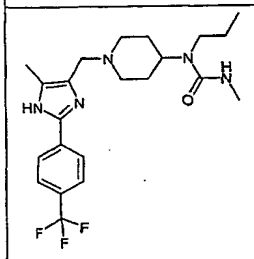
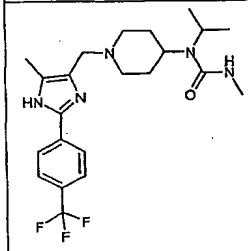
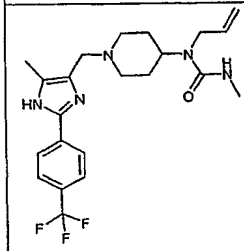
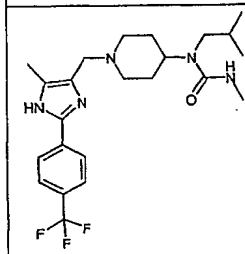
	1-Benzyl-3-[4-(trifluoromethyl)phenyl]1-[1-[[2-[4-(trifluoromethyl)phenyl-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1,3-Dibenzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-3-cyclohexyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-3-tert.-butyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(2-phenylethyl)urea

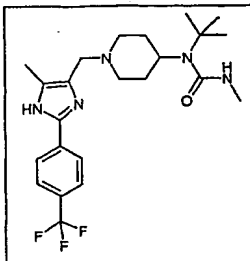
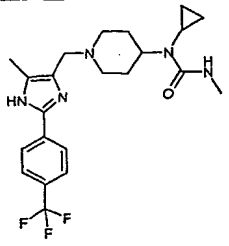
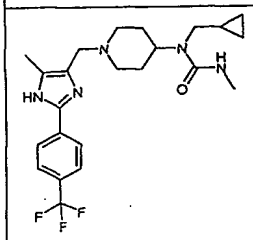
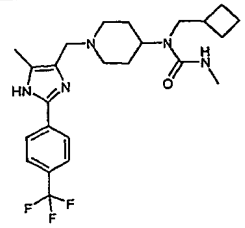
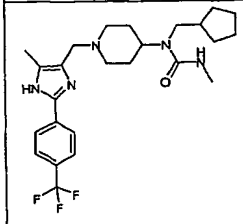
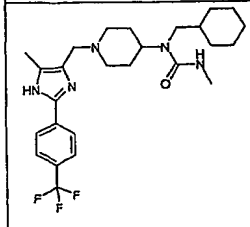
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3-phenylpropyl)urea
	1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-(2,4,6-trimethoxybenzyl)-3-methylurea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(2-methylphenyl)urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3-methylphenyl)urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-methylphenyl)urea

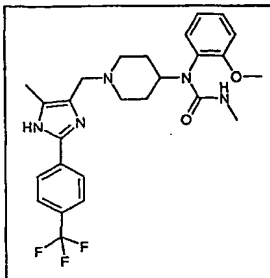
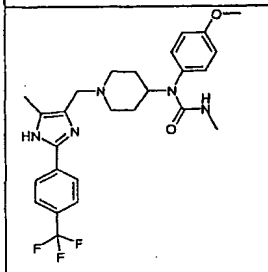
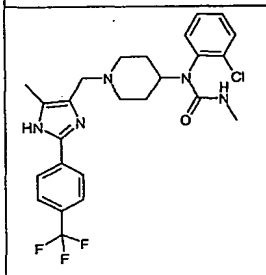
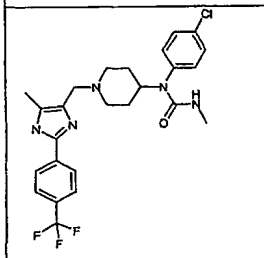
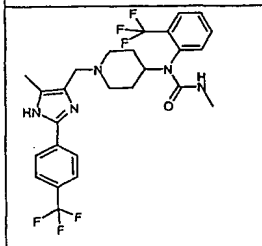
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3,4-dimethylphenyl)urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3,5-dimethylphenyl)urea
	1-Benzyl-3-(2-chlorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-3-(3-chlorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-3-(3,5-dichlorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea

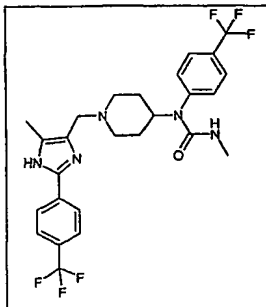
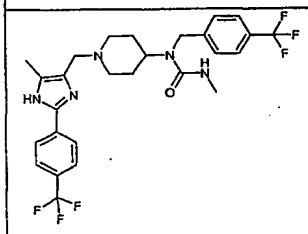
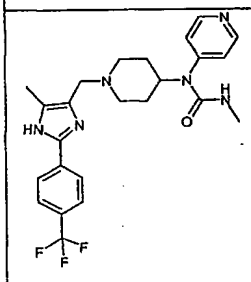
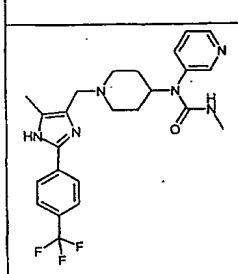
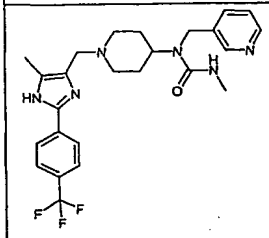
	1-Benzyl-3-(4-fluorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-[4-(dimethylamino)phenyl]urea
	1-Benzyl-3-(4-cyanophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-nitrophenyl)urea
	1-Benzyl-3-(3-bromophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea

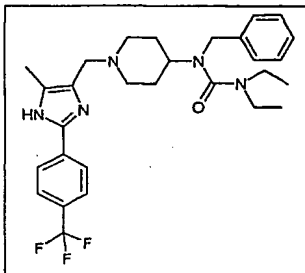
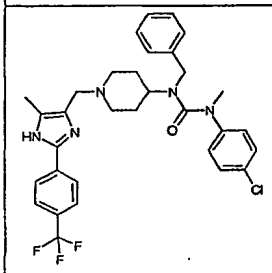
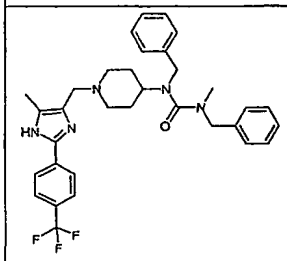
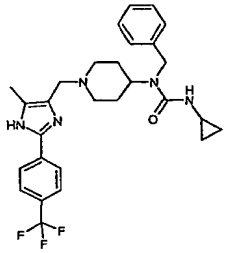
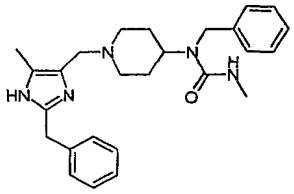
	1-Benzyl-3-[3-(trifluoromethyl)phenyl]-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea
	1-[1-[[2-(2-Methoxyphenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea
	Methyl 5-[[4-(1-benzyl-3-methylureido)piperidino]methyl]-2-[4-(trifluoromethyl)phenyl]-3H-imidazole-4-carboxylate
	1-Benzyl-1-[1-[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-ylmethyl]-4-piperidinyl]-3-phenylurea
	1-Methyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea

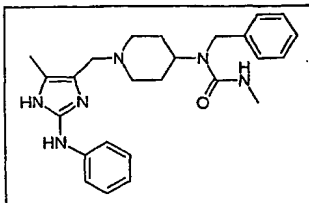
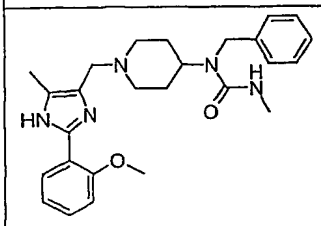
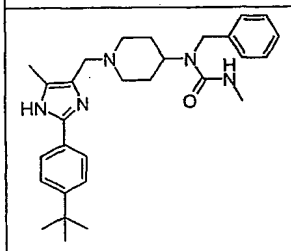
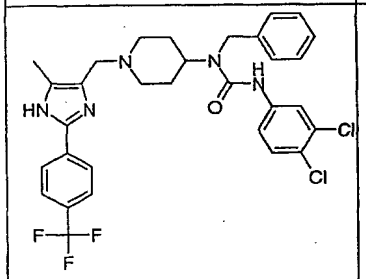
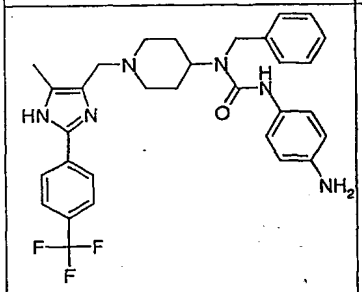
	1-Ethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-propyl-urea
	1-Isopropyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Allyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Isobutyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea

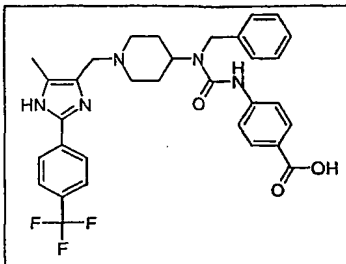
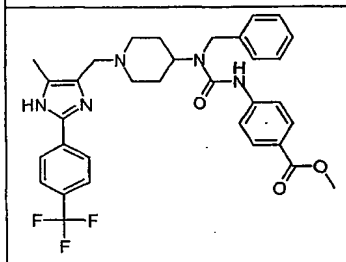
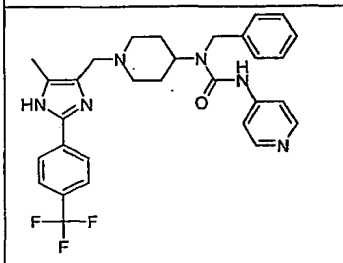
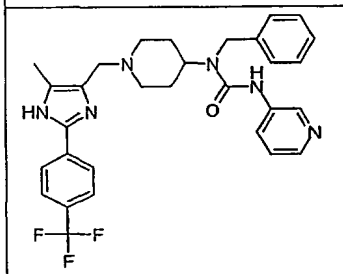
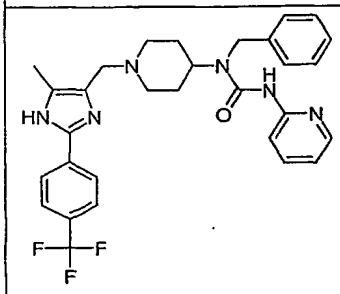
	1-tert.-butyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea.
	1-Cyclopropyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Cyclopropylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Cyclobutylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Cyclopentylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Cyclohexylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea

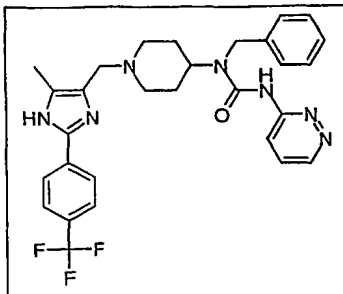
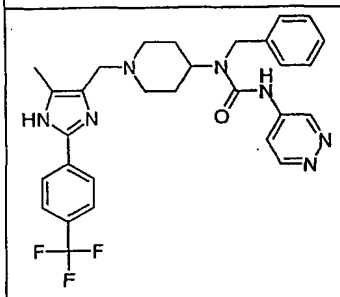
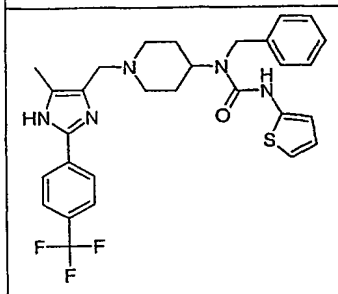
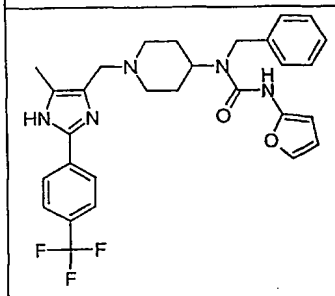
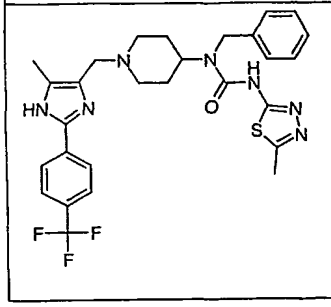
	1-(2-Methoxy-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-(4-Methoxy-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-(2-Chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-(4-Chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(2-trifluoromethyl-phenyl)-urea

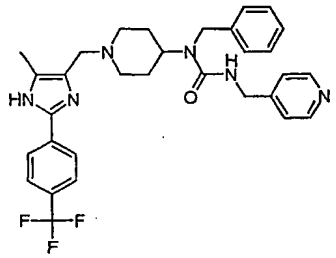
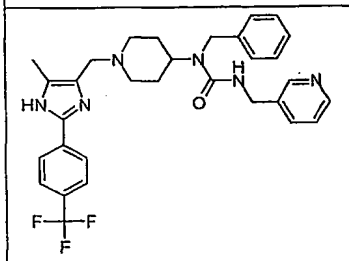
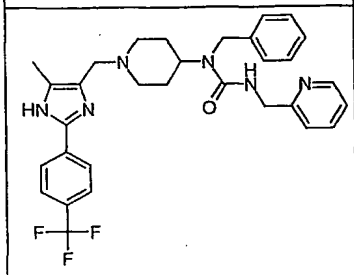
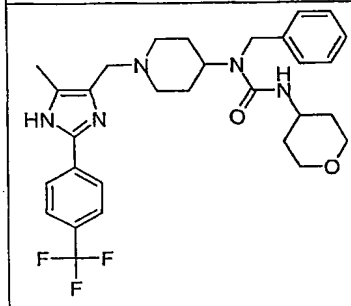
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-trifluoromethyl-phenyl)-urea
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-trifluoromethyl-benzyl)-urea
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-4-yl-urea
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-3-yl-urea
	3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-3-ylmethyl-urea

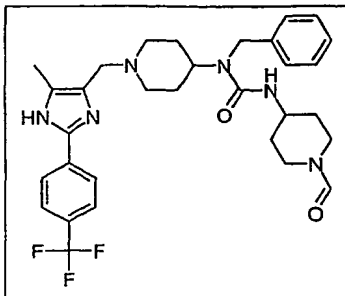
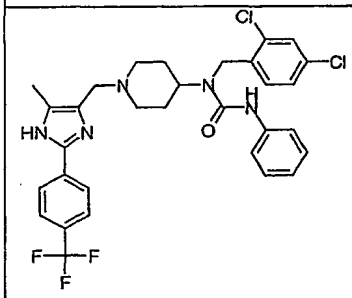
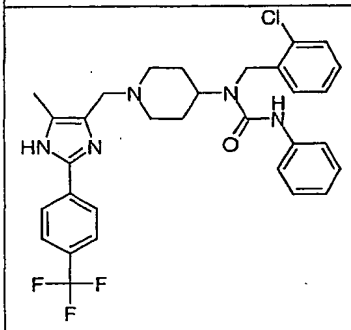
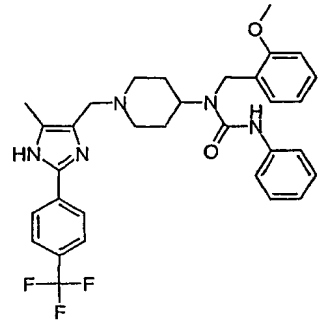
	1-Benzyl-3,3-diethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Benzyl-3-(4-chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1,3-Dibenzyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Benzyl-3-cyclopropyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Benzyl-1-[1-(2-benzyl-5-methyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-3-methyl-urea

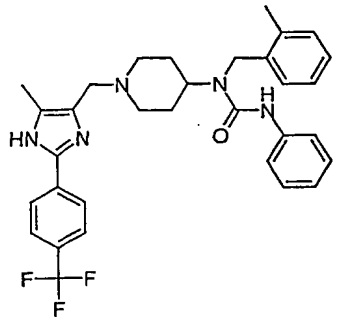
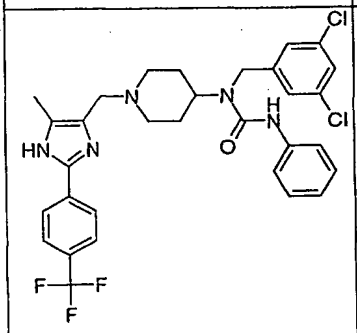
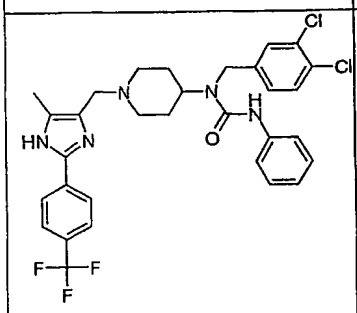
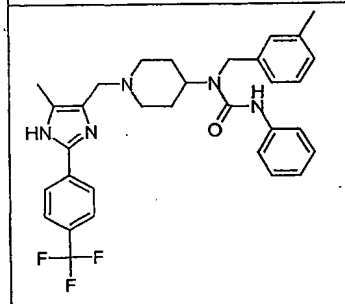
	1-Benzyl-3-methyl-1-[1-(5-methyl-2-phenylamino-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-urea
	1-Benzyl-1-{1-[2-(2-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea
	1-Benzyl-1-{1-[2-(4-tert.-butyl-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea
	1-Benzyl-3-(3,4-dichloro-phenyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	3-(4-Amino-phenyl)-1-benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea

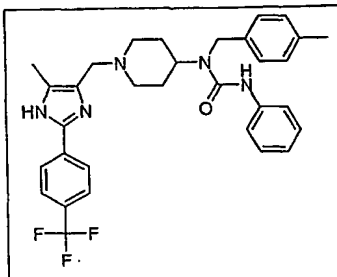
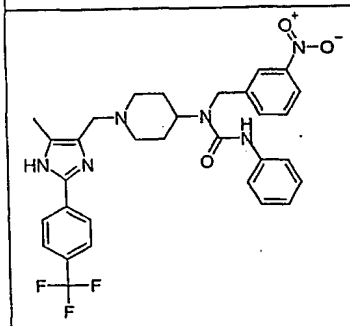
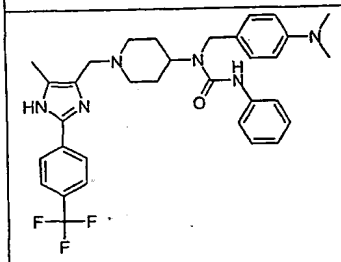
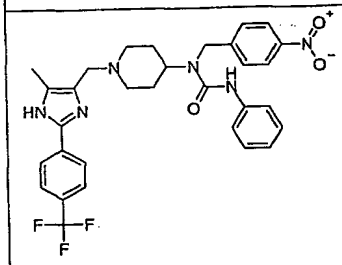
	4-(3-Benzyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-ureido)-benzoic acid
	4-(3-Benzyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-ureido)-benzoic acid methyl ester
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-4-yl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-3-yl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-2-yl-urea

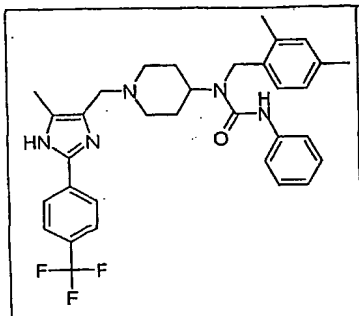
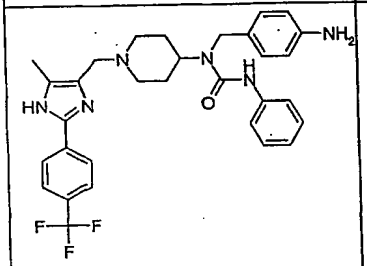
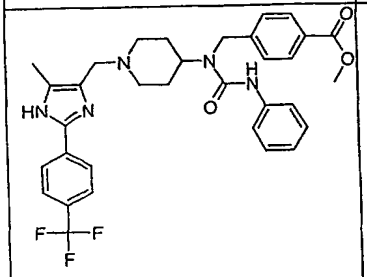
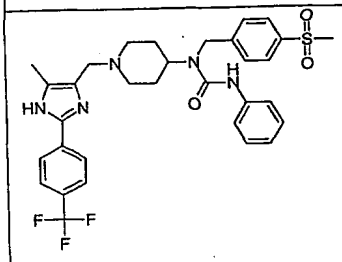
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridazin-3-yl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridazin-4-yl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-thiophen-2-yl-urea
	1-Benzyl-3-furan-2-yl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-Benzyl-3-(5-methyl-[1,3,4]thiadiazol-2-yl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea

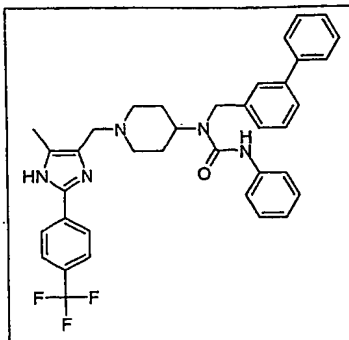
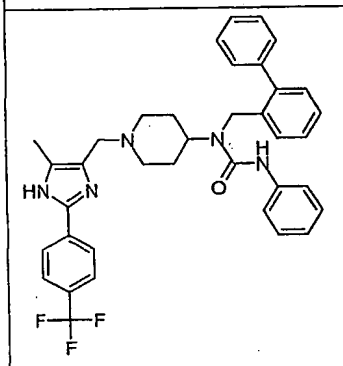
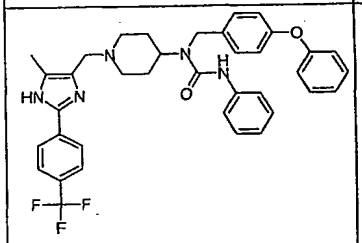
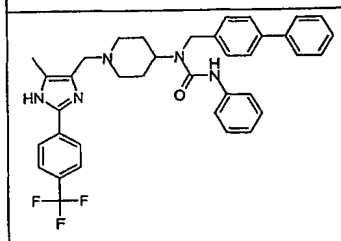
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-4-ylmethyl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-3-ylmethyl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-2-ylmethyl-urea
	1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-(tetrahydro-pyran-4-yl)-urea

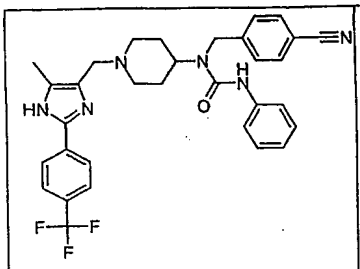
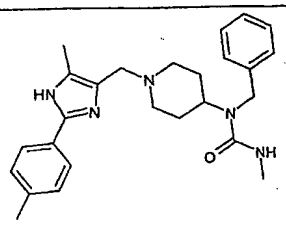
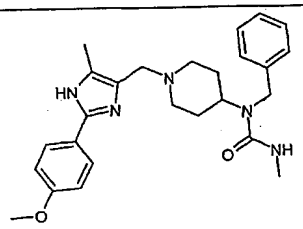
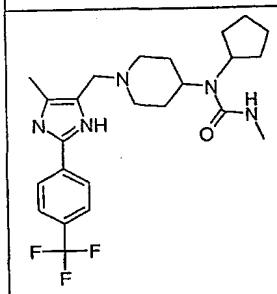
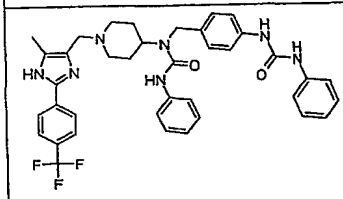
	1-Benzyl-3-(1-formyl-piperidin-4-yl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-(2,4-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-(2-Chloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-(2-Methoxy-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea

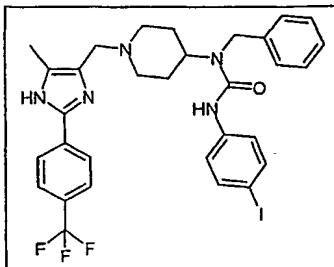
	1-(2-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-(3,5-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-(3,4-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-(3-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea

	1-(4-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(3-nitro-benzyl)-3-phenyl-urea
	1-(4-Dimethylamino-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-nitro-benzyl)-3-phenyl-urea

	1-(2,4-Dimethyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-(4-Amino-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	4-(1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-ureidomethyl)-benzoic acid methyl ester
	1-(4-Methanesulfonyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea

	1-Biphenyl-3-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-Biphenyl-2-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-phenoxy-benzyl)-3-phenyl-urea
	1-Biphenyl-4-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea

	1-(4-Cyano-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea
	1-Benzyl-3-methyl-1-[1-(5-methyl-2-p-tolyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-urea
	1-Benzyl-1-{1-[2-(4-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea
	1-Cyclopentyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea
	1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-1-[4-(3-phenyl-ureido)-benzyl]-urea

	1-Benzyl-3-(4-iodo-phenyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea

Chemokines and their receptors are potent activators and chemoattractants for leukocyte subpopulations and some non-hemopoietic cells. Whilst more studies are needed to delineate in more detail which chemokines and receptors are important in different diseases, they have been implicated in autoimmune disease [Arimilli et al Immunol. Rev. 177, 43-51 (2000)], diseases such as allergy, psoriasis, atherosclerosis, and malaria [Murdoch et al., Blood 95, 3032-3043 (2000)], multiple sclerosis [Zhang et al., Mult. Scler. 6, 3-13 (2000)], renal disease [Wada et al., Clin. Exp. Nephrol. 4, 273-280 (2000)], as well as in allograft rejection [Hancock et al., Curr. Opin. Immunol. 12, 511-516. (2000)].

CCR5, specifically, is believed to be the major coreceptor involved in sexual, parenteral and vertical transmission of HIV [van't Wout et al., J. Clin. Invest. 94, 2060-2067 (1994); Cornelissen, et al J.Virol. 69, 1810-1818 (1995); Veenstra et al., Clin. Infect. Dis. 21, 556-560 (1995)]. CCR5, specifically, may also have an etiological role in colitis [Ajuebor et al., J. Immunol. 166, 552-558 (2001)], multiple sclerosis [Simpson et al., J. Neuroimmunol. 108, 192-200 (2000)], diabetes [Cameron et al., J. Immunol. 165, 1102-1110 (2000)] and Alzheimer's disease [Xia and Hyman, Journal of Neurovirology 5, 32-41 (1999)].

The aminopiperidine derivatives provided by the present invention are useful in the treatment of the human or animal body. They can be used as medicaments, especially for treating viral diseases (HIV, HCV, and HBV infection), immune mediated conditions or diseases, bacterial diseases, parasitic diseases, inflammatory diseases, hyperproliferative vascular diseases, as anti-depressants, for the treatment of tumors, and cancer and to prevent allograft rejection. Especially, the present aminopiperidine derivatives are therapeutically active substances in the prevention and treatment of infection by the human immunodeficiency virus (HIV) and can be used as medicaments for the treatment of such diseases.

In particular, compounds of the present invention, and pharmaceutical compositions containing the same, are useful as chemotherapeutic agents, inhibitors of viral replication and modulators of the immune system. They can be used for the treatment of diseases mediated by retroviruses such as the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV replication such as protease inhibitors, reverse transcriptase inhibitors and fusion inhibitors or with pharmacoenhancers such as cytochrome P450 inhibitors.

The aminopiperidine derivatives provided by the present invention can be used alone, or in combination with other therapeutically active agents, for example, an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-

parasitic agent, an anti-inflammatory agent, an anti-fungal agent and/or an anti-vascular hyperproliferation agent.

Compounds, whenever prepared by the processes of the present invention are also an object of the present invention.

Assay Method:

Resonance energy transfer assay (RET):

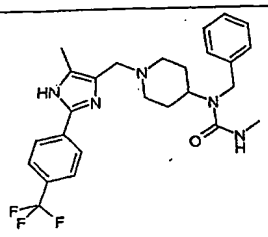
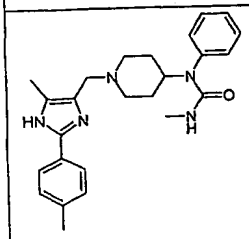
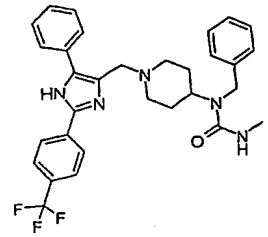
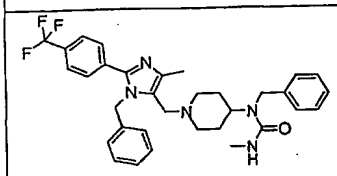
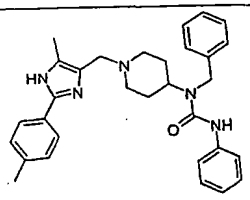
The activity of the compounds was determined using a fusion assay developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the macrophage-tropic primary isolate HIV-1JRFL and PM1 cells as previously described (Litwin, V et al (1996) "Human immunodeficiency virus type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer" J Virol 70(9), 6437-6441). The following minor modifications were applied: the assay buffer used comprised PBS/15%FCS (filtered through a 0.2uM filter); cells were not washed three times in PBS before reading; all compounds were tested in a final concentration of 1% DMSO, and the monoclonal antibody Leu3a (330ng/mL) was added to each plate, as a positive control (for 100% inhibition of cell fusion).

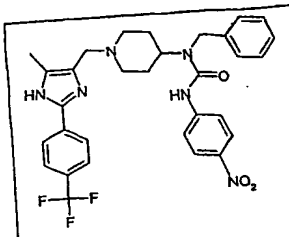
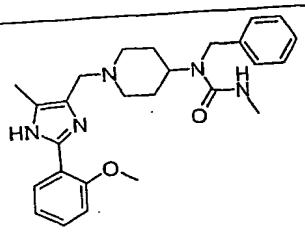
gp120-sCD4-CCR5 binding assay:

The gp120-sCD4-CCR5 binding assay was carried out as previously described (Dragic, T., A. Trkola, et al. (2000). "A binding pocket for a small molecule inhibitor of HIV-1 entry within the transmembrane helices of CCR5." Proc Natl Acad Sci U S A 97: 5639-44.) with the following minor modifications: the cell line used for these experiments was a CHO-K1 cell line stably transfected with the human CCR5 gene; the gp120-CD4 complex comprised recombinant biotinylated gp120 (JRFL strain) and soluble recombinant CD4; and all compounds were tested in a final concentration of 1% DMSO.

All reagents and cell lines were obtained from Progenics Pharmaceuticals Inc, Tarrytown, NY, USA, and are commercially available or can be prepared according to the methods described and the information given in the papers above.

In the assay, compounds of the formulas I range in activity from an IC_{50} of about 0.5 to about 1500 nM, with preferred compounds having a range of activity from about 0.5 to about 750 nM, more preferably about 0.5 to 300 nM, and most preferably about 0.5 to 50 nM.

Stucture	Name	FACS IC_{50} (μM)
	1-Benzyl-3-methyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea	0.11
	3-Methyl-1-[1-[[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylurea	0.18
	1-Benzyl-3-methyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea	19.1
	1-Benzyl-1-[1-[[3-benzyl-5-methyl-2-[4-(trifluoromethyl)phenyl]-3H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea	1.1
	1-Benzyl-1-[1-[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-ylmethyl]-4-piperidinyl]-3-phenylurea	0.03

	1-Benzyl-1-[1-{[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-nitrophenyl)urea	0.45
	1-Benzyl-1-{1-[2-(2-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea	9.6

The aminopiperidine derivatives provided by the present invention, as well as their pharmaceutically useable salts, can be used as medicaments in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally, either orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions, syrups, or suspensions, or rectally, e.g. in the form of suppositories. They can also be administered parenterally (intramuscularly, intravenously, or subcutaneously), e.g. in the form of injection solutions, or nasally, e.g. in the form of nasal sprays.

For the manufacture of pharmaceutical preparations, the aminopiperidine derivatives, as well as their pharmaceutically useable salts, can be formulated with a therapeutically inert, inorganic or organic excipient for the production of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions.

Suitable excipients for tablets, coated tablets, dragées, and hard gelatin capsules are, for example, lactose, corn starch and derivatives thereof, talc, and stearic acid or its salts.

Suitable excipients for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols.

Suitable excipients for injection solutions are, for example, water, saline, alcohols, polyols, glycerine or vegetable oils.

Suitable excipients for suppositories are, for example, natural and hardened oils, waxes, fats, semi-liquid or liquid polyols.

Suitable excipients for solutions and syrups for enteral use are, for example, water, polyols, saccharose, invert sugar and glucose.

The pharmaceutical preparations of the present invention may also be provided as sustained release formulations or other appropriate formulations.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavourants, salts for adjustment of the osmotic pressure, buffers, masking agents or antioxidants.

The pharmaceutical preparations may also contain other therapeutically active agents known in the art.

The aminopiperidine derivatives provided by the present invention are useful in the treatment of immune mediated conditions and diseases, viral diseases, bacterial diseases,

parasitic diseases, inflammatory diseases, hyperproliferative vascular diseases, allograft rejection, tumours, and cancers.

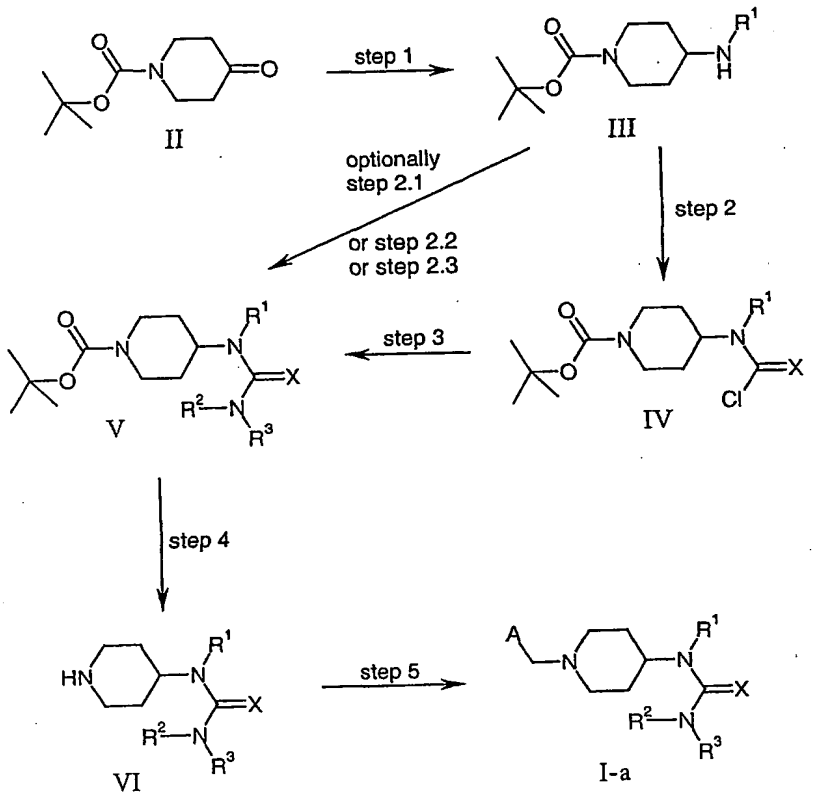
The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. For oral administration, a daily dosage of between about 0.01 and about 100 mg/kg body weight per day should be appropriate in monotherapy and/or in combination therapy. A typical preparation will contain from about 5% to about 95% active compound (w/w) . The daily dosage can be administered as a single dosage or in divided dosages, typically between 1 and 5 dosages per day.

The aminopiperidine derivatives provided by the present invention or the medicaments thereof may be used in monotherapy or combination therapy, i.e. the treatment may be in conjunction with the administration of one or more additional therapeutically active substance(s). When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the aminopiperidine derivatives of the present invention. Concurrent administration, as used herein thus includes administration of the agents at the same time or at different times.

It will be understood that references herein to treatment extend to prophylaxis as well as to treatment of existing conditions. Treatment of a disease or condition, as used herein, also includes preventing, inhibiting, regressing, reversing, alleviating or relieving the disease or condition, or the clinical symptoms thereof. The term "subject" as used herein refers to animals, including humans and other mammals.

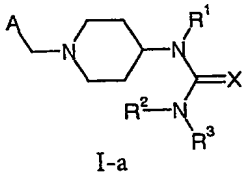
The compounds of the present invention can be prepared as shown in the following schemes:

Reaction scheme 1:



wherein R^1, R^2, R^3, X and A are as defined for compounds of formula I.

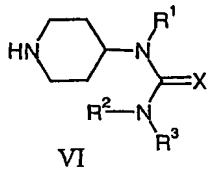
Also part of the present invention is the preparation of compounds of formula I-a



I-a

which process comprises

reacting a compound of formula VI



VI

a) with a carboxaldehyde of formula A-CHO,

wherein A are as defined in formula I

and subsequently reducing the reaction product with a reducing agent; or

b) with a methylene halide of formula A-CH_2Hal,

wherein R^1, R^2, R^3, A and X are as defined in formula I and Hal is Cl, Br or I.

The reaction represents step 5 of reaction scheme 1 and is described in more detail below.

In reaction scheme 1, step 1 is the reaction of an N-protected piperidone derivative of formula II (commercially available) with an amine of formula R^1NH_2, wherein R^1 is as defined for compounds of formula I (commercially available or synthesised according to known methods from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) in the presence of an appropriate reducing agent and, optionally, an appropriate acid to obtain aminopiperidine derivative of formula III as described in the literature, for example in Ryder et al., Bioorg Med Chem Lett, 9, 2453-8 (1999), or Abdel-Magid et al., J Org Chem, 61, 3849-62 (1996).

Appropriate reducing agents for the reaction are known from the art and are, for example, lithium aluminium hydride, sodium borohydride, sodium cyanoborohydride or diisobutylaluminium hydride, and, preferably, sodium triacetoxyborohydride, and appropriate acids are carboxylic acids such as acetic acid or mineral acids such as hydrochloric acid. The reaction is carried out in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or a mixture of the aforementioned solvents, preferably dichoromethane at a reaction temperature from

0°C to the boiling temperature of the reaction mixture, most preferably at ambient temperature.

The reaction can also be carried out under a hydrogen atmosphere in the presence of an appropriate catalyst (for example, a palladium catalyst such as palladium on charcoal). This reaction is carried out in an organic solvent, preferably at ambient temperature.

Alternatively, the imine can be pre-formed and subsequently reduced using a reducing agent such as sodium triacetoxyborohydride or under a hydrogen atmosphere in the presence of an appropriate catalyst as described above.

In reaction scheme 1, the N-tert.-butoxycarbonyl protecting group of the derivative of formula II can be replaced by other known N-protecting groups, for example those known from 'Protecting groups in organic synthesis' 3rd Ed. T. W. Greene, P. G. M. Wuts; Wiley-Interscience, New York 1999.

In step 2 of reaction scheme 1, an aminopiperidine derivative of formula III is converted to the corresponding piperidinecarbamoyl chloride or piperidinethiocarbamoyl chloride derivative of formula IV as, for example, described in Tsai et al., Biorg Med Chem, 7, 29-38 (1999).The reaction to obtain the piperidinecarbamoyl chloride is conveniently carried out with diphosgene, triphosgene or, preferably, phosgene, and the reaction to obtain the piperidinethiocarbamoyl chloride is carried out with dithiophosgene, trithiophosgene or thiophosgene in the presence of a base such as potassium carbonate, sodium carbonate, magnesium carbonate, calcium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, magnesium hydrogen carbonate or calcium hydrogen carbonate, preferably sodium hydrogen carbonate. The reaction is carried out at a reaction temperature from -20°C to the boiling temperature of the reaction mixture, preferably at a reaction temperature between -10°C and 60°C, most preferably at 0°C. Appropriate solvents for the reaction are inert organic solvents such as ethers (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), halogenated hydrocarbons (e.g. dichloromethane or trichloromethane), hydrocarbons (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene) or mixtures of the aforementioned solvents, preferably a mixture of dichloromethane and saturated aqueous sodium hydrogen carbonate.

In step 3 of reaction scheme 1, a piperidinecarbamoyl chloride derivative of formula IV is reacted with HNR^2R^3, wherein R^2 and R^3 are as defined for compounds of formula I, to obtain a piperidinylurea derivative of formula V. The reaction is carried out using methods similar to those described in for example, Richard C. Larock; Comprehensive Organic Transformations: a guide to functional group preparations, 2nd Edition, 1999,

John Wiley and Sons, Inc., New York or J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons, for example by combining the reagents in an appropriate solvent at a reaction temperature from -20°C to the boiling temperature of the reaction mixture, preferably at a reaction temperature between -10°C and 60°C, most preferably at 0°C. Appropriate solvents for the reaction are ethers (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), hydrocarbons (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), halogenated hydrocarbons (e.g. dichloromethane or trichloromethane), polar aprotic solvents (e.g. dimethylsulfoxide, N,N-dimethylacetamide or N,N-dimethylformamide) or a mixture of the aforementioned solvents. Preferred solvents for the reaction are the aforementioned ethers, most preferably tetrahydrofuran.

Optionally, steps 2 and 3 of reaction scheme 1 can be replaced by step 2.1 of the reaction scheme, by following the reaction conditions described in step 1 of reaction scheme 7 (synthesis *via* isocyanate and isothiocyanate derivatives). The preferred solvent for this reaction is dichloromethane and the reaction is preferably carried out at ambient temperature.Alternatively, derivative V can be obtained either by reacting derivative III with a suitably activated carbamate (step 2.2), or by converting derivative III into an activated carbamate derivative and reacting this with an appropriate amine (step 2.3). The reactions may be carried out as described in the literature, for example in Lagu et al., J Med Chem, 42, 4794-803 (1999), Rodriguez et al., J Med Chem, 27, 1222-1225 (1984), Sen et al., IzvAkad Nauk SSSR, Ser Khim, 3, 548-51 (1993), Corriu et al., J Organomet Chem, 419, 9-26 (1991), and Takatari et al., J Med Chem, 32, 56-64 (1989).

In step 4 of reaction scheme 1, the protecting group of the piperidinylurea derivative of formula V is cleaved in the presence of trifluoroacetic acid to obtain the deprotected piperidinylurea derivative of formula VI. Alternatively, the reaction can be carried out with other acids as described in 'Protecting groups in organic synthesis' 3rd Ed. T. W. Greene, P. G. M. Wuts; Wiley-Interscience, New York 1999 (examples of other acids are: hydrochloric acid, acetyl chloride/methanol, *p*-toluene sulphonic acid, sulphuric acid, trimethylsilyl iodide, trimethylsilyltrifluoromethanesulphonate, methanesulphonic acid, boron trifluoride diethyl etherate, cerium ammonium nitrate). The reaction is conveniently carried out in an organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane) or a mixture of the aforementioned solvents. Preferred solvents for the reaction are the aforementioned halogenated hydrocarbons; the most preferred solvent is dichloromethane. The reaction is carried out at a reaction temperature from -20°C to the boiling temperature of the

reaction mixture, preferably at a reaction temperature between -10°C and 60°C, most preferably between 0°C and 60°C.

In step 5 of reaction scheme 1, the deprotected piperidinyl urea derivative of formula VI is reacted with a carboxaldehyde of formula A-CHO, wherein A is as defined for compounds of formula I (commercially available or synthesised according to known methods from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons), and subsequently reduced with an appropriate reducing agent, to obtain the 1-substituted piperidinyl urea of formula I-a. Appropriate reducing agents for the reaction are known from the art and are, for example, lithium aluminium hydride, sodium cyanoborohydride or diisobutylaluminium hydride, and, preferably, sodium triacetoxyborohydride. The reaction is carried out in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or a mixture of the aforementioned solvents, preferably dichloromethane, at a reaction temperature from 0°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

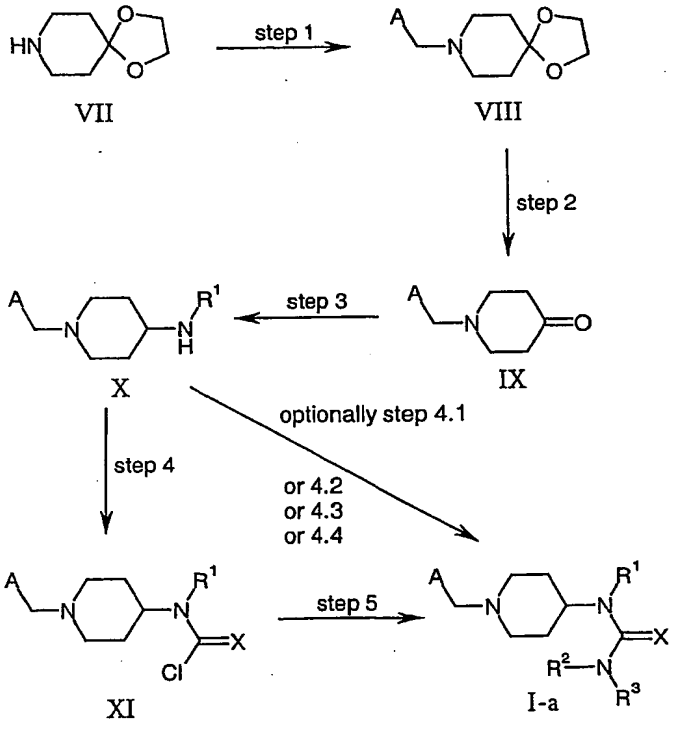
The reaction can also be carried out under a hydrogen atmosphere in the presence of an appropriate catalyst (for example a palladium catalyst such as palladium on charcoal). This reaction is carried out in an organic solvent, preferably at ambient temperature.

Alternatively, the imine can be pre-formed and subsequently reduced using a reducing agent such sodium triacetoxyborohydride or under a hydrogen atmosphere in the presence of an appropriate catalyst as described above.

An alternative method of carrying out step 5 of reaction scheme 1 is to react a deprotected piperidinyl urea derivative of formula VI with a halo compound of formula A-CH_2Hal wherein A is as defined for compounds of formula I and Hal is chlorine, bromine or iodine, preferably chlorine to obtain a 1-substituted piperidinyl urea of formula I-a. Compounds of formula A-CH_2Hal are commercially available or can be synthesized according to methods known in the art, for example via conversion of an alcohol to the corresponding chloride with e.g. thionyl chloride or according to other methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons), The reaction is optionally carried out in the presence of an appropriate base and in an appropriate solvent. Appropriate bases are, for example, potassium carbonate, sodium carbonate, magnesium carbonate, calcium carbonate, potassium hydroxide, sodium hydroxide, magnesium hydroxide, calcium hydroxide or N(C_{1-4}-alkyl)$_3$, wherein

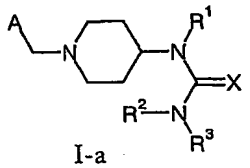
different or the same C_{1-4}-alkyl groups are attached to the N-atom. Examples of the aforementioned amines are $N(CH_3)_3$, $N(C_2H_5)_3$, $N(isoC_3H_7)_3$ and, preferably, $N(C_2H_5)(isoC_3H_7)_2$. The reaction is carried out in an appropriate inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene) or a mixture of the aforementioned solvents, preferably dicholoromethane, at a reaction temperature from 0°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

Reaction scheme 2:



wherein R^1, R^2, R^3, X and A are as defined for compounds of formula I.

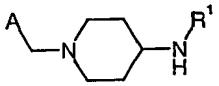
In accordance with the present invention, the preparation of compounds of formula I-a



I-a

which process comprises

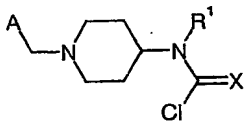
reacting a compound of formula X



X

a) with phosgene or thiophosgene of formula $X=CCl_2$,

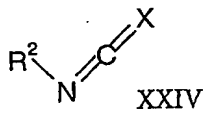
to obtain compound of formula XI



XI

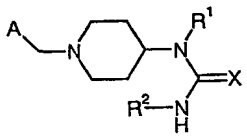
and subsequently reacting compound of formula XI with HNR^2R^3; or

b) with a compound of formula XXIV,



XXIV

and further reacting the compound of formula I-b



I-b

obtained with R^3-Hal,

wherein R^1, R^2, R^3, A and X are as defined for compounds of formula I and Hal is chlorine or bromine.

The reaction represents step 4 and 5 of reaction scheme 2 or step 1 of reaction scheme 7 and is described in more detail below.

In reaction scheme 2, step 1 is carried out in the same manner as that described for step 5 of reaction scheme 1 in that a protected piperidinone of formula VII (commercially available) is reacted with a carboxaldehyde of formula A-CHO, wherein A is as defined for compounds of formula I, and subsequently reduced with an appropriate reducing agent, to obtain a 1-substituted piperidine derivative of formula VIII. The compounds of formula A-CHO are commercially available or can be synthesised according to other known methods from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons).

In step 1 of reaction scheme 2, the protected piperidinyl derivative of formula VII is reacted with a carboxaldehyde of formula A-CHO, wherein A is as defined for compounds of formula I (commercially available or synthesised according to known methods from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons), and subsequently reduced with an appropriate reducing agent, to obtain the substituted piperidinyl of formula VIII. Appropriate reducing agents for the reaction are known from the art and are for example lithium aluminium hydride, sodium cyanoborohydride or diisobutylaluminium hydride, and, preferably, sodium triacetoxyborohydride. The reaction is carried out in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbons (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or a mixture of the aforementioned solvents, preferably dichloromethane, at a reaction temperature from 0°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

The reaction can also be carried out under hydrogen atmosphere in the presence of an appropriate catalyst (for example a palladium catalyst such as palladium on charcoal). This reaction is carried out in an organic solvent, preferably at ambient temperature.

Alternatively, the imine can be pre-formed and subsequently reduced using a reducing agent such as sodium triacetoxyborohydride or under a hydrogen atmosphere in

the presence of an appropriate catalyst or under transfer hydrogenation conditions such as ammonium formate or cyclohexadiene in the presence of a palladium catalyst as described above.

An alternative method of carrying out step 1 of reaction scheme 2 is to react a protected piperidinyl derivative of formula VII with a halo compound of formula A-CH_2Hal wherein A is as defined for compounds of formula I and Hal is chlorine, bromine or iodine, preferably chlorine to obtain a 1-substituted piperidinyl of formula VIII. Compounds of formula A-CH_2Hal are commercially available or can be synthesized according to methods known in the art, for example via conversion of an alcohol to the corresponding chloride with e.g. thionyl chloride or according to other methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons), The reaction is optionally carried out in the presence of an appropriate base and in an appropriate solvent. Appropriate bases are, for example, potassium carbonate, sodium carbonate, magnesium carbonate, calcium carbonate, potassium hydroxide, sodium hydroxide, magnesium hydroxide, calcium hydroxide or N(C_{1-4}-alkyl)$_3$, wherein different or the same C_{1-4}-alkyl groups are attached to the N-atom. Examples of the aforementioned amines are N(CH_3)$_3$, N(C_2H_5)$_3$ or N(isoC_3H_7)$_3$. The reaction is carried out in an appropriate inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene) or a mixture of the aforementioned solvents, preferably dicholoromethane, at a reaction temperature from 0°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

In step 2 of reaction scheme 2, the protected ketone function of the compound of formula VIII is deprotected in the presence of an appropriate acid to obtain the1-substituted-piperidin-4-one of formula IX. Appropriate acids for the deprotection reaction are mineral acids, tosic acid, and Lewis acids, as described for example in 'Protecting groups in organic synthesis' 3rd Ed. T. W. Greene, P. G. M. Wuts; Wiley-Interscience, New York 1999. Examples of suitable acids are, pyridinium tosylate, acetic acid, perchloric acid, bromodimethylborane, trimethylsilyl iodide, titanium(IV) chloride, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, samarium(III) chloride, sodium iodide/cesium(III) chloride), preferably mineral acids, most preferably hydrochloric acid. The reaction is carried out in water or in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), an alcohol (e.g.

methanol, ethanol, propanol, butanol, octanol or cyclohexanol), a polar aprotic solvent (e.g. dimethylsulfoxide N,N-dimethylacetamide or N,N-dimethylformamide) or a mixture of the aforementioned organic solvents. The reaction temperature is preferably between -20°C and the boiling temperature of the reaction mixture, preferably between 50°C and 150°C and most preferably between 80°C and 120°C.

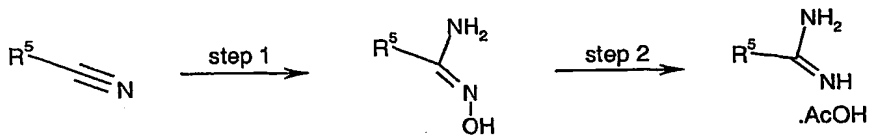
In step 3 of reaction scheme 2, the reaction is carried out in the same manner as described for the first step of reaction scheme 1 in that a 1-substituted- piperidinone of formula IX is reacted with an amine of formula R^1NH_2, wherein R^1 is as defined for compounds of formula I, in the presence of an appropriate reducing agent and an appropriate acid to obtain an aminopiperidine derivative of formula X. The amines of formula R^1NH_2 are commercially available or can be synthesised according to known methods from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) Alternatively, as in step 5 of reaction scheme 1, the imine can be pre-formed and subsequently reduced using a reducing agent such as sodium triacetoxyborohydride or under a hydrogen atmosphere in the presence of an appropriate catalyst as described above.

In step 4 of reaction scheme 2, an aminopiperidine derivative of formula X is converted to the corresponding piperidinecarbamoyl chloride derivative of formula XI as for example described in Tsai et al., Biorg Med Chem, 7, 29-38 (1999). The reaction is carried out as described for step 2 in reaction scheme 1.

In step 5 of reaction scheme 2, a piperidinecarbamoyl chloride derivative of formula XI is reacted with HNR^2R^3, wherein R^2 and R^3 are as defined for compounds of formula I, to obtain piperidine compound of formula I-a. The reaction is carried out as described for step 3 in reaction scheme 1. Optionally, steps 4 and 5 of reaction scheme 2 can be replaced by step 4.1 of the reaction scheme, by following the reaction conditions described in step 1 of reaction scheme 7 (synthesis *via* isocyanate and isothiocyanate derivatives). The preferred solvent for this reaction is dichloromethane and the reaction is preferably carried out at ambient temperature. Alternatively, derivative I-a can be obtained either by reacting derivative III with a suitably activated carbamate (step 4.2), or by converting derivative III into an activated carbamate derivative and reacting this with an appropriate amine (step 4.3). The reactions may be carried out as described in the literature, for example in Lagu et al., J Med Chem, 1999, 42, 4794-803; Rodriguez et al., J Med Chem, 27, 1222-1225, (1984); Sen et al., IzvAkad Nauk SSSR, Ser Khim, 3, 548-51, (1993); Corriu et al., J Organomet Chem, 1991, 419, 9-26; Takatari et al., J Med Chem, 32, 56-64, (1989). Alternatively, compound of formula Ib may be obtained by reacting a suitable carbamoyl chloride,

prepared according to the French patent FR2234293, and a compound of formula X (step 4.4).

Reaction scheme 3:



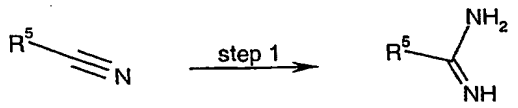
XII XIII XIV

wherein R^5 is as defined for compounds of formula I.

In reaction scheme 3, step 1 is the reaction of a nitrile derivative of formula XII (commercially available or synthesized according to known methods in textbooks on organic chemistry, for example J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) with hydroxylamine hydrochloride and an appropriate base to obtain an amidoxime of formula XIII as, for example, described in Judkins et al., Syn Com, , 26, 4351-67,(1996). Appropriate bases for the reaction are potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, magnesium carbonate, calcium carbonate, potassium hydroxide, sodium hydroxide, magnesium hydroxide, calcium hydroxide and alkoxides, preferably sodium carbonate, and most preferably potassium tert.-butoxide The reaction is conveniently carried out in water or an organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene, an alcohol (e.g. methanol, ethanol, propanol, butanol, octanol or cyclohexanol), a polar aprotic solvent (e.g. dimethylsulfoxide , N,N-dimethylacetamide or N,N-dimethylformamide), or a mixture of the aforementioned organic solvents, preferably the aforementioned alcohols and most preferably methanol or ethanol. The reaction temperature is preferably between -20°C to the boiling temperature of the reaction mixture, preferably between 30°C and 150°C and most preferably between 50°C and 130°C.

In step 2 of reaction scheme 3, the amidoxime of formula XIII is converted to the corresponding amidine acetate of formula XIV as, for example, described in Judkins et al., Syn Com, , 26, 4351-67, (1996). The amidoxime is dissolved in an alcoholic solvent or a carboxylic acid, preferably acetic acid and reacted with acetic anhydride or, optionally carboxylic acids, under reductive conditions for example in the presence of a palladium catalyst (e.g. palladium on charcoal) under a hydrogen atmosphere, or under transfer hydrogenation conditions for example ammonium formate or cyclohexadiene and a palladium catalyst (e.g. palladium on charcoal) or other reducing agents known in the art. Different reaction conditions, for example using tin(II) chloride and hydrogen chloride would lead to the corresponding amidine hydrochlorides. Alternatively, the amidines of formula XIV can be prepared by reduction of the corresponding nitro and nitroso compounds as, for example described in J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons. The reaction is preferably carried out at a reaction temperature between -20°C and the boiling temperature of the reaction mixture, preferably between 0°C and 70°C and most preferably at ambient temperature.

Reaction scheme 4:



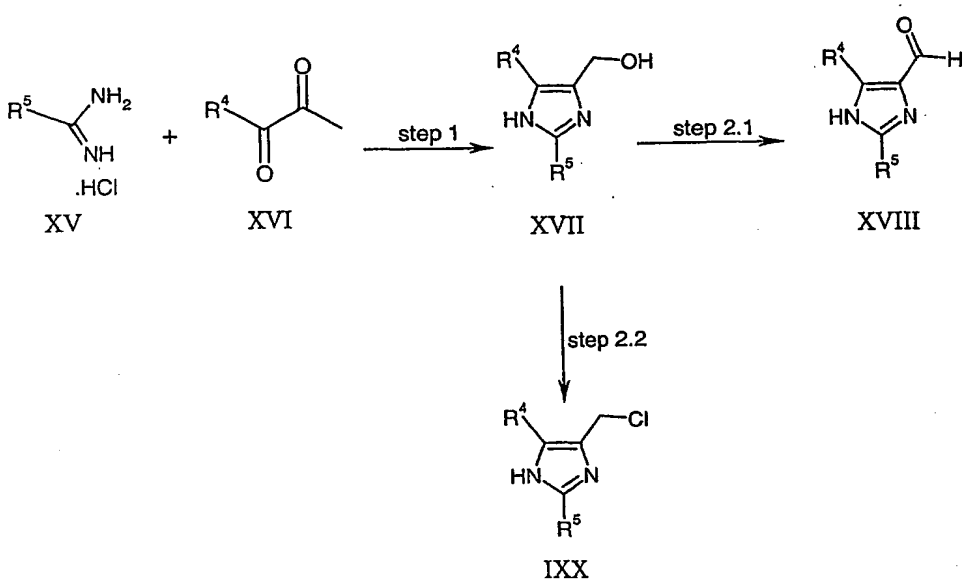
XII XV .HCl

wherein R^5 is as defined for compounds of formula I.

In reaction scheme 4, a nitrile derivative of formula XII (commercially available or synthesized according to known methods in textbooks on organic chemistry, for example J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) is reacted with ammonium chloride in the presence of an appropriate base as, for example, described in Moss et al., JACS, 107, 2743-8, (1985) to obtain an amidine hydrochloride of formula XV. Appropriate bases for the reaction are alkoxides, preferably methoxide, most preferably sodium methoxide. The reaction is conveniently carried out in an inert organic solvent such as a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl

cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), alcohols (e.g. methanol, ethanol, propanol, butanol, octanol or cyclohexanol), or a mixture of the aforementioned inert organic solvents, preferably the aforementioned alcohols and most preferably methanol. The reaction is preferably carried out at a reaction temperature between -20°C and the boiling temperature of the reaction mixture, preferably between 0°C and 70°C and most preferably at ambient temperature.

Reaction scheme 5:



XV XVI XVII XVIII

IXX

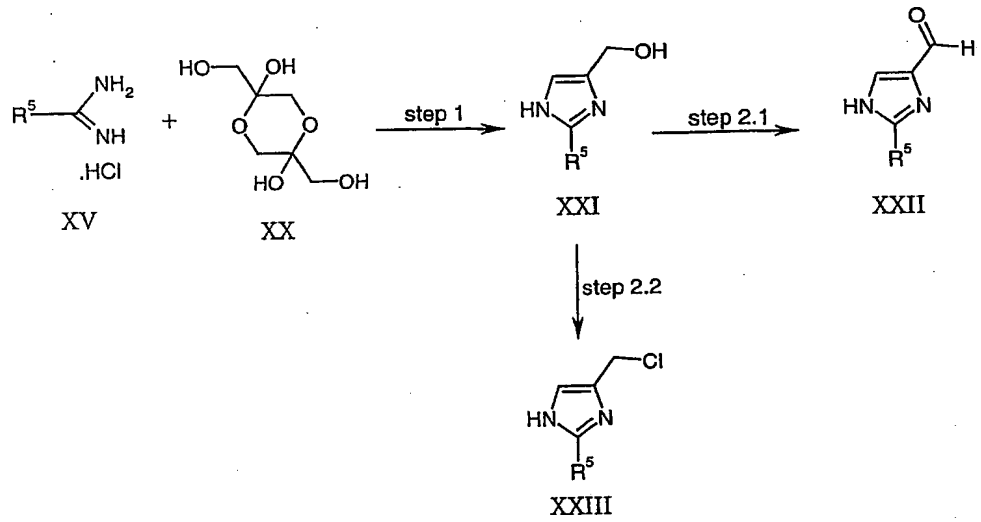
wherein R^5 is as defined for compounds of formula I and R^4 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl, wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, or substituted heterocyclyl are substituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens.

In reaction scheme 5, step 1 is the reaction of an amidine hydrochloride of formula XV or an amidine acetate of formula XIV with a dione derivative of formula XVI (commercially available or synthesized according to known methods in textbooks on organic chemistry, for example J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) in the presence of an appropriate base, followed by reaction with an appropriate acid to obtain a substituted imidazole compound of formula XVII as described in the literature, for example in US Patent 4,126,444 or McNab et al., JCS. Perkin Trans 1, 15, 2203-2210, (1993). The reaction is conveniently carried out, firstly, at a reaction temperature from -20°C to 50°C, preferably 0°C and subsequently (for the acidic reaction) at a reaction temperature between 50°C and the boiling temperature of the reaction mixture, preferably at the boiling temperature of the reaction mixture. Appropriate bases for the reaction are, for example, potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, magnesium carbonate, calcium carbonate, caesium carbonate, potassium hydroxide, sodium hydroxide, magnesium hydroxide, calcium hydroxide, preferably sodium hydroxide. Appropriate acids for the subsequent reaction are mineral acids (e.g. hydrochloric acid, sulphuric acid, and perchloric acid), carboxylic acids (e.g. acetic acid), and *p*-toluenesulphonic acid, preferably hydrochloric acid. Further, the reaction is carried out in water or an organic solvent such as an alcohol (e.g. methanol, ethanol, propanol, butanol, octanol or cyclohexanol), a polar aprotic solvent (e.g. dimethylsulfoxide, N,N-dimethylacetamide or N,N-dimethylformamide), water or a mixture of the aforementioned organic solvents, preferably water.

In step 2.1 of reaction scheme 5, the hydroxy-methyl group of the substituted imidazole compound of formula XVII is oxidized with an appropriate oxidizing agent to obtain the corresponding aldehyde imidazole compound of formula XVIII. The reaction is carried out according to any known method of oxidation of a benzylic alcohol to the corresponding benzylic aldehyde, for example Swern (oxalyl chloride and dimethyl sulphoxide), Dess-Martin periodinane, tetrapropyl ammonium perruthernate or pyridinium chlorochromate. The reaction is conveniently carried out with manganese dioxide as oxidizing agent in a non-oxidizable organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene or a mixture of the aforementioned organic solvents, preferably 1, 4-dioxane. The reaction temperature is preferably between -78°C and the boiling temperature of the reaction mixture, preferably between 50°C and 140°C and most preferably between 60°C and 120°C.

In step 2.2 of reaction scheme 5, a hydroxymethyl-substituted imidazole compound of formula XVII is treated with an appropriate chlorinating agent to obtain the corresponding chloromethyl-substituted imidazole compound of formula IXX. The reaction is carried out according to known methods for converting a hydroxymethyl group into the corresponding chloromethyl group, for example by treatment with chlorinating agents such as thionyl chloride, oxalyl chloride, phosphorus trichloride, phosphorus pentachloride, and triphenyl phosphine/carbon tetrachloride, preferably thionyl chloride. The reaction is optionally carried out in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or a mixture of the aforementioned organic solvents, preferably with no added solvent. The reaction temperature is preferably between 78°C and the boiling temperature of the reaction mixture, preferably between 50°C and 140°C and most preferably between 60°C and 120°C.

Reaction scheme 6:



wherein R^5 is as defined for compounds of formula I.

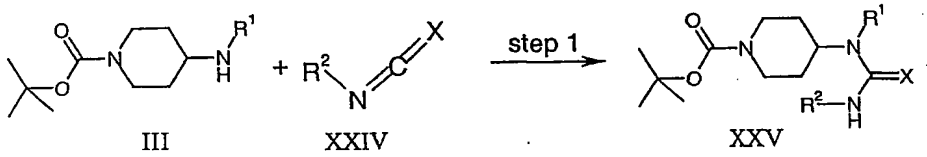
In reaction scheme 6, step 1 is the reaction of an amidine hydrochloride of formula XV or an amidine acetate of formula XIV with 1, 3-dihydroxyacetone dimer of formula

XX to obtain an imidazole compound of formula XXI, as described, for example, in Thurkauf et al., J Med Chem, 38, 2251-2255, (1995). The reaction is carried out in the presence of liquid ammonia or an ammonia solution, preferably 0.880 ammonia solution at a reaction temperature between -80°C and the boiling temperature of the reaction mixture, preferably between 70°C and 90°C, and most preferably at 80°C.

In step 2.1 of reaction scheme 6, the hydroxymethyl group of a substituted imidazole compound of formula XXI is oxidized with an appropriate oxidizing agent to obtain the corresponding aldehyde imidazole compound of formula XXII. The reaction is carried out as described for step 2.1 in reaction scheme 5.

In step 2.2 of reaction scheme 6, the hydroxymethyl group of a substituted imidazole compound of formula XXI is converted to the corresponding chloromethyl group by treatment with an appropriate chlorinating agent to obtain the corresponding chloromethyl-imidazole compound of formula XXIII. The reaction is carried out as described for step 2.2 in reaction scheme 5.

Reaction scheme 7:



III XXIV XXV

wherein R^1, R^2 and X are as defined for compounds of formula I.

In reaction scheme 7, an aminopiperidine derivative of formula III is reacted with an isothiocyanate or isocyanate of formula XXIV (commercially available or synthesized according to known methods in textbooks on organic chemistry, for example J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) to give a piperidinyl thiourea or a piperidinyl urea derivative of formula XXV. Appropriate solvents for the reaction are organic solvents such as ethers (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), halogenated hydrocarbons (e.g. dichloromethane or trichloromethane), hydrocarbons (e.g. cyclohexane, methyl

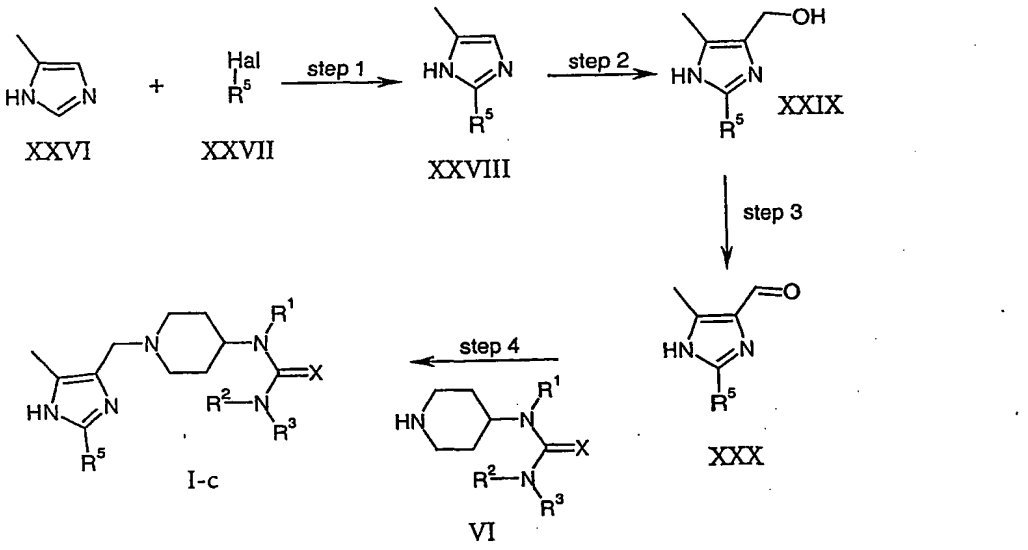
cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), alcohols (e.g. methanol, ethanol, propanol, butanol, octanol or cyclohexanol), or a mixture of the aforementioned organic solvents, preferably dichloromethane or a mixture of toluene and ethanol. The reaction is carried out at a reaction temperature from -20°C to the boiling temperature of the reaction mixture, preferably at a reaction temperature between 0°C and 110°C, most preferably at ambient temperature for dichloromethane and between 60°C and 100°C for toluene/ethanol.

An alternative method for the synthesis of a piperidinyl thiourea or a piperidinyl urea derivative of formula XXV is the reaction of an aminopiperidine derivative of formula III with a suitably activated thiocarbamate or carbamate.

Optionally, the NHR^2-function of a piperidinyl thiourea or a piperidinyl urea derivative of formula XXV may be reacted with R^3-Hal, wherein R^3 is as defined for compounds of formula I and Hal is chlorine or bromine, according to methods known in the art, for example Hoffmann-alkylation, to obtain a piperidine compound of formula V. This reaction is known from textbooks on organic chemistry for example J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons.

Piperidinyl thiourea or piperidinyl urea derivatives of formula XXV are subsequently deprotected as described in step 4 of reaction scheme 1

Reaction scheme 8:



wherein R^1, R^2, R^3 and X are as defined for compounds of formula I, and R^5 is C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens; and wherein substituted aryl means aryl substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and wherein substituted heterocyclyl issubstituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens and wherein Hal is fluorine, chlorine, bromine or iodine.

In reaction scheme 8, step 1 is the reaction of a substituted imidazole derivative of formula XXVI with a chloride derivative of formula XXVII in an appropriate solvent followed by reaction with an appropriate base, to obtain a substituted imidazolyl phenyl methanone derivative of formula XXVIII as, for example described in Bastiaansen et al., Synthesis, 675-6, (1978). The reaction of the substituted imidazole derivative of formula XXVI with the chloride derivative of formula XXVII is carried out under an inert atmosphere such as a nitrogen or argon atmosphere in the presence of a base such as pyridine or a tertiary amine (e.g. trimethylamine, triethylamine, and tripropylamine) Optionally, an inert organic solvent such as a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or a mixture of the aforementioned mentioned solvents may be used. Preferably, the reaction is carried out using a mixture of pyridine and triethylamine as the solvent. This part of the reaction is conveniently carried out at a reaction temperature from -20°C to 70°C, preferably at ambient temperature. Appropriate bases for the second part of the reaction are potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, magnesium carbonate, calcium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide, magnesium hydroxide, and calcium hydroxide, preferably sodium hydroxide. An appropriate solvent is water. This part of the reaction is carried out at a reaction temperature between 50°C and the boiling temperature of the reaction mixture, preferably at the boiling temperature of the reaction mixture.

The reaction may be carried out as described above or according to Gompper et al., Chem Ber, , 92, 550 (1959) or Hlasta et al., Bioorg Med Chem Lett, 7, 89-94, (1997).

In step 2 of reaction scheme 8, a substituted imidazolyl derivative of formula XXVIII is reacted with formaldehyde or paraformaldehyde in the presence of an appropriate base to obtain the corresponding substituted imidazolyl methanol compound of formula XXIX, as for example described in Watson et al., Syn Com, 22, 2971-7, (1992). Appropriate bases for the reaction are potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, magnesium carbonate, calcium carbonate, cesium carbonate, potassium hydroxide, sodium hydroxide, magnesium hydroxide, and calcium hydroxide, preferably sodium hydroxide. The reaction is preferably carried out at a reaction temperature between -20°C and the boiling temperature of the reaction mixture, preferably between 0°C and 100°C and most preferably at a reaction temperature between 30°C and 70°C. Further, the reaction is carried out in water or an organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), pyridine, an alcohol (e.g. methanol, ethanol, propanol, butanol, octanol or cyclohexanol) or a mixture of the aforementioned solvents, preferably water and ethanol.

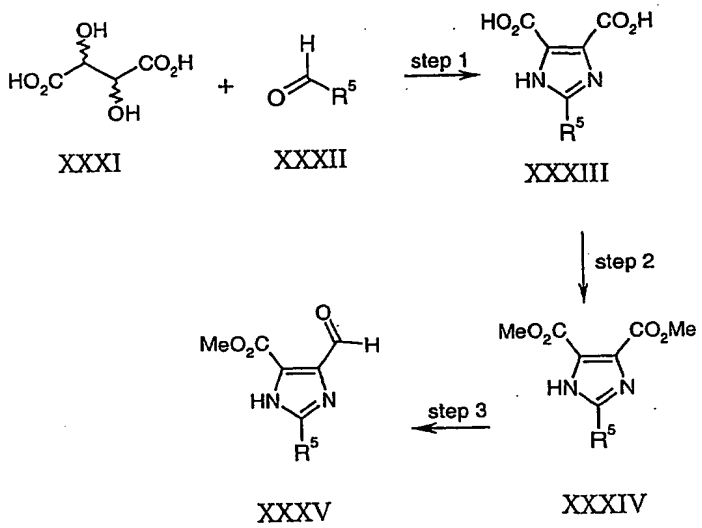
In step 3 of reaction scheme 8, a substituted imidazole methanol compound of formula XXIX is oxidized with an appropriate oxidizing agent to obtain the corresponding imidazole aldehyde compound of formula XXX. The reaction is carried out as described for step 2.1 in reaction scheme 5.

In step 4 of reaction scheme 8, an imidazole aldehyde compound of formula XXX is reacted with a piperidine derivative of formula VI (synthesized as described in reaction scheme 1 or by deprotection of compound XXV from reaction scheme 7) to obtain a piperidinylurea of formula I-c. The reaction is carried out as described for step 5 in reaction scheme 1.

If R^5 in a compound of formula I-c is an optionally substituted phenyl-carbonylgroup the carbonyl group may be reduced with an appropriate reducing agent to the corresponding phenylhydroxymethyl group as, for example, described in Ooi & Suschitzy, J Chem Soc, 2871(1982). Appropriate reducing agents are sodium borohydride, lithium aluminium hydride, di-isobutyl aluminium hydride, alane (preparation *in situ* according to methods known in the art), or other hydride reducing reagents known in the art, preferably sodium borohydride. The reaction is carried out at a reaction temperature between -78°C and the boiling temperature of the reaction mixture, preferably between 0°C and 70°C, and most preferably at ambient temperature. Further, the reaction is carried out in an organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene,

m-xylene or p-xylene), pyridine, an alcohol (e.g. methanol, ethanol, isopropanol, butanol, octanol or cyclohexanol), a polar aprotic solvents (e.g. dimethylsulfoxide , N,N-dimethylacetamide or N,N-dimethylformamide), or a mixture of the aforementioned organic solvents, preferably isopropyl alcohol.

Reaction scheme 9:



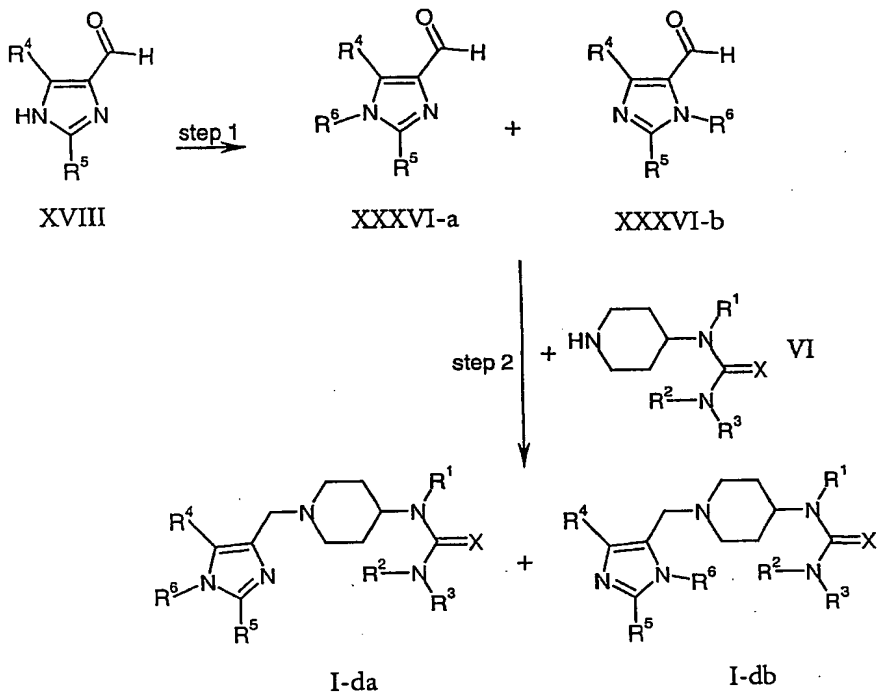
wherein R^5 is C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl, or substituted heterocyclyl,wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens,;and wherein substituted aryl means aryl substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens; and wherein substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens.

In reaction scheme 9, step 1 is the reaction of racemic tartaric acid of formula XXXI (commercially available) with concentrated nitric acid, followed by fuming nitric acid and sulfuric acid at a reaction temperature from 10°C to 60°C, preferably at a reaction temperature from 20°C to 50°C. The reaction mixture is subsequently cooled to a temperature from –20°C to 0°C, preferably –10°C, to obtain a solid intermediate which is reacted with a substituted aldehyde derivative of formula XXXII (commercially available or synthesised according to methods known in the art) at a pH of 6 to 8, preferably 7, in the presence of ammonia solution, preferably concentrated ammonia solution, to obtain a phenyl-substituted imidazole derivative of formula XXXIII. The reaction temperature is preferably in the range of –20°C to 20°C, more preferably in the range of –10°C to 10°C. This type of reaction is described by MacKinnon et al in Tetrahedron, 54, 9837-48, (1998).

In step 2 of reaction scheme 9, the dicarboxylic acid derivative of formula XXXIII is esterified using a lower alcohol, for example methanol, in the presence of an appropriate mineral acid, to obtain the corresponding diester of formula XXXIV. The esterification reaction is carried out according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons. Appropriate acids for the esterification reaction are mineral acids (e.g. hydrochloric acid and sulphuric acid), and *p*-toluenesulphonic acid, preferably sulphuric acid. The reaction is carried out at a reaction temperature between ambient temperature to the boiling temperature of the reaction mixture, preferably at the boiling temperature of the reaction mixture, optionally in the presence of an organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane) or a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene).

In step 3 of reaction scheme 9, the diester of formula XXXIV is treated with an appropriate reducing agent to obtain the corresponding formyl imidazole compound of formula XXXV. Appropriate reducing agents for the reaction are known from the art and are for example diisobutylaluminiumhydride. The reaction is carried out in the presence of sodium hydride in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, toluene, o-xylene, m-xylene or p-xylene) or a halogenated aromatic hydrocarbon, at a reaction temperature between -78°C andthe boiling temperature of the reaction mixture, preferably starting at a reaction temperature between 50°C andthe boiling temperature of the reaction mixture (after the addition of sodium hydride) and at a temperature between -78°C and 0°C for the addition of the reducing agent. This type of reaction is known in the art and is, for example, carried out as described in WO 9119715.

Reaction scheme 10:



wherein R^1, R^2, R^3, R^4, R^5 and X are as defined for compounds of formula I, and wherein R^6 is C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, COR, CO_2R; wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl or heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens; and wherein substituted aryl are substituted with 1-5 substituents and substituted heterocyclyl are substituted with 1-4 substituents, these substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens.

In reaction scheme 10, step 1 is the reaction of an imidazole compound of formula XVIII with R^6-Hal, wherein R^6 is as defined above and Hal is Cl, Br, F or I (commercially available or synthesised according to known methods from textbooks on organic

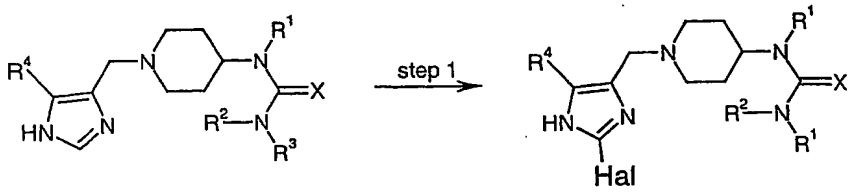
chemistry e.g. from J. March (1992), "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th ed. John Wiley and Sons) in the presence of an appropriate base to obtain a mixture of the corresponding N-alkylated or arylated imidazole. Appropriate bases for the reaction are known from the art and are for example tertiary amines, carbonates (e.g.sodium carbonate, magnesium carbonate, calcium carbonate or cesium carbonate), alkyl lithiums (e.g. methyl lithium or ethyl lithium), metal hydrides (e.g. sodium hydride, lithium hydride or calcium hydride), preferably sodium hydride. The reaction is carried out in an inert organic solvent such as a polar aprotic solvents (e.g. dimethylsulfoxide , N,N-dimethylacetamide or N,N-dimethylformamide , an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a chlorinated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or mixtures of the aforementioned solvents, preferably dimethyl formamide. The reaction is carried out at a reaction temperature from -20°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

In step 2 of reaction scheme 10, the substituted imidazole derivative of formula XXXVI-a and XXXVI-b is reacted with a piperidine derivative of formula VI and subsequently reduced with an appropriate reducing agent to obtain the substituted piperidinyl derivatives of formula I-da and I-db. Appropriate reducing agents for the reaction are known from the art and are, for example, sodium cyanoborohydride or diisobutylaluminium hydride, preferably sodium triacetoxyborohydride. The reaction is carried out in an inert organic solvent such as an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a halogenated hydrocarbon (e.g. dichloromethane or trichloromethane), a hydrocarbon (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), or a mixture of the aforementioned solvents, preferably dichloromethane, at a reaction temperature from 0°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

The reaction can also be carried out under hydrogen atmosphere in the presence of an appropriate catalyst (for example a palladium catalyst such as palladium on charcoal). This reaction is carried out in an organic solvent, preferably at ambient temperature.

Alternatively, the imine can be pre-formed and subsequently reduced using a reducing agent such as sodium triacetoxyborohydride or under a hydrogen atmosphere in the presence of an appropriate catalyst as described above.

Reaction scheme 11:



I-e I-f

wherein R^1, R^2, R^3, R^4, and X are as defined for compounds of formula I and Hal is chlorine, bromine or iodine.

In step 1 of reaction scheme 11, an imidazole derivative of formula I-e (commercially available or synthesized according to the methods described before) is treated with chlorine, bromine or iodine, preferably iodine, in the presence of an appropriate base to obtain the corresponding iodo-imidazole derivative of formula I-f. Appropriate bases for the reaction are known from the art and are, for example, carbonates (e.g. sodium carbonate, magnesium carbonate, potassium carbonate or cesium carbonate), hydrogen carbonates (e.g. sodium hydrogen carbonate or potassium hydrogen carbonate), hydroxides (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide or barium hydroxide), preferably sodium hydroxide. The reaction is carried out in an inert organic solvent such as a polar aprotic solvents (e.g. dimethylsulfoxide, N,N-dimethylacetamide or N,N-dimethylformamide, an ether (e.g. tetrahydrofuran, diethyl ether, dibutyl ether or dioxane), a chlorinated hydrocarbon (e.g. dichloromethane or trichloromethane), hydrocarbons (e.g. cyclohexane, methyl cyclohexane, decaline, benzene, toluene, o-xylene, m-xylene or p-xylene), an alcohol (e.g. methanol, ethanol, propanol, butanol, octanol or cyclohexanol), or a mixture of the aforementioned solvents, preferably a mixture of dichloromethane and water. The reaction is carried out at a reaction temperature from -20°C to the boiling temperature of the reaction mixture, preferably at ambient temperature.

The following examples illustrate the present invention:

In the following examples the abbreviations used have the following significations:

min	minute(s)
h	hour(s)
d	day(s)

DMAW 120 denotes asolvent mixture containing dichloromethane, methanol, acetic acid and water in the ratio 120:15:3:2 respectively

DMAW 240 denotes a solvent mixture containing dichloromethane, methanol, acetic acid and water in the ratio 240:24:32:21 respectively

All temperatures are given in degrees Celsius (°C).

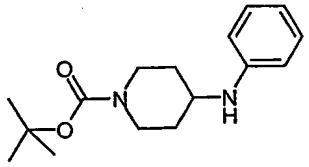
Mass spectra were recorded under electron impact conditions on a THERMOQUEST MAT95 S with a source temperature of 200°C. or under electrospray ionization spectra conditions, on either a THERMOQUEST SSQ 7000 [Solvent 0.085% TFA in 90% Acetonitrile/water; flow rate 100 microliters/min; capillary 250°C; spray voltage 5KV; sheath gas 80 psi], or an LC-MS system (liquid chromatograph coupled to mass spectrum) THERMOQUEST TSQ 7000 ELECTROSPRAY or MICROMASS PLATFORM ELECTROSPRAY [Solvent 0.1% TFA in water or 0.085% TFA in 90% acetonitrile/ water or 0.085% TFA in acetonitrile]. With regard to the known starting materials, some of these may be purchased from commercial suppliers. Catalogue numbers for commercially available starting materials are provided. Other known starting materials and their analogues can be prepared by methods well known in the art. Examples of compounds available from commercial suppliers, and citations to the synthesis of other compounds and their analogues are provided in the following:

Compounds, whenever prepared by the processes of the present invention are also an object of the present invention.

Examples according to reaction scheme 1:

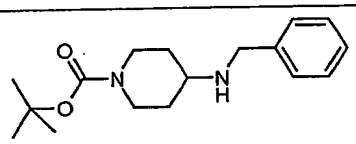
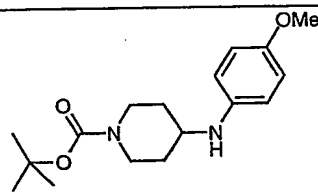
Reaction scheme 1, step 1

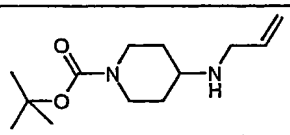
4-Phenylamino-piperidine-1-carboxylic acid tert.-butyl ester



A solution of N-tert-butoxycarbonyl-4-piperidone (Lancaster 13361, 7g) and aniline (Aldrich 24228-4, 3.3g) in dichloromethane (200ml) was treated with sodium triacetoxyborohydride (Aldrich 31639, 10.4g) followed by acetic acid (2.1g) and the mixture stirred for 2 h at ambient temperature. 1M Aqueous sodium hydroxide solution (100ml) was added, followed by diethyl ether (200ml) and the mixture stirred vigorously for 5 min. The organic phase was separated, washed with water (100ml), followed by brine (100ml), dried (anhydrous magnesium sulphate), filtered and evaporated to give the title compound as a white solid (9.5g, 98%). Mass spectrum 277 $[M+H]^+$.

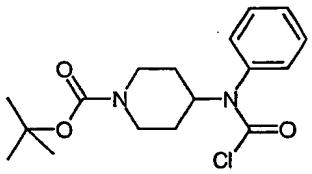
The following compounds were produced in a manner analogous to that described above, by replacing aniline with the appropriate amine

Systematic name	Structure	m/z $[M + H]^+$
4-Benzylamino-piperidine-1-carboxylic acid tert.-butyl ester		291
4-(4-Methoxy-phenylamino)-piperidine-1-carboxylic acid tert.-butyl ester		307

4-Allylamino-piperidine-1-carboxylic acid tert.-butyl ester		241

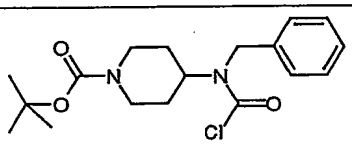
Reaction Scheme 1, Step 2

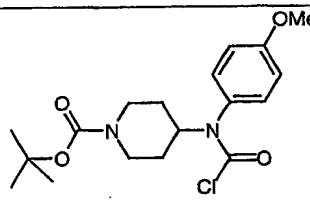
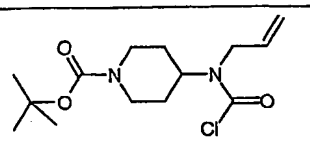
4-Phenylaminocarbamoylchloride-piperidine-1-carboxylic acid tert.-butyl ester



To a rapidly stirring, ice-cold solution of 4-phenylamino-piperidine-1-carboxylic acid tert.-butyl ester (5g) in dichloromethane (500ml) and saturated aqueous sodium hydrogen carbonate solution (400ml) was added 20% phosgene in toluene (Fluka 79380,, 50ml). After 1 h the organic phase was separated, dried (anhydrous magnesium carbonate), filtered and evaporated to give the title compound as a pale yellow solid (6.2g, 100%). Mass spectrum 339 $[M+H]^+$.

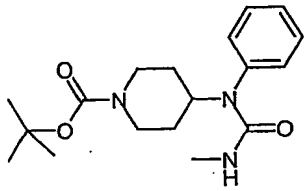
The following compounds were produced in a manner analogous to that described above by replacing the 4-phenylamino-piperidine-1-carboxylic acid tert.-butyl ester with an appropriate amine:

Name	Structure	m/z $[M + H]^+$
4-Benzylcarbamylchloride-piperidine-1-carboxylic acid tert.-butyl ester		353

4-(4-Methoxy-phenylcarbamylchloride)-piperidine-1-carboxylic acid tert.-butyl ester		369
4-Allylcarbamyl chloride-piperidine-1-carboxylic acid tert.-butyl ester		303

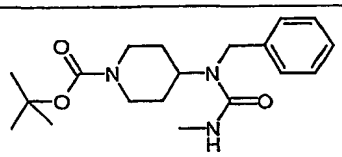
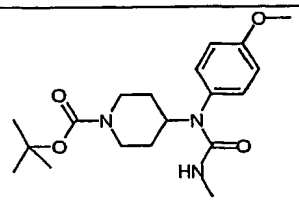
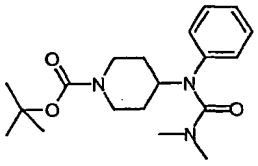
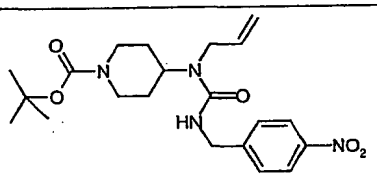
Reaction scheme 1, Step 3

4-(3-Methyl-1-phenyl-ureido)-piperidine-1-carboxylic acid tert.-butyl ester



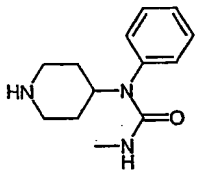
To an ice-cold solution of methylamine (Fluka 65590, 33% in ethanol, 2.5ml) in ethanol (30ml) was added, slowly, a solution of 4-phenylaminocarbamoyl chloride-piperidine-1-carboxylic acid tert.-butyl ester (3g) in tetrahydrofuran (10ml) and the mixture allowed to stir for 1 h. The volatile solvents were removed under reduced pressure and the residue partitioned between dichloromethane (40ml) and water (30ml). The organic layer was separated, dried (anhydrous magnesium sulphate), filtered and evaporated. The residue was recyrstallized from toluene to give the title compound as a white, crystalline solid (2.1g, 71%). Mass spectrum 334 $[M+H]^+$.

The following compounds were produced in a manner analogous to that described above, by replacing methylamine with the appropriate amine and the 4-phenylaminocarbamoyl chloride-piperidine-1-carboxylic acid tert.-butyl ester with the appropriate carbamoyl chloride:

Systematic name	Structure	m/z $[M + H]^+$
4-(1-Benzyl-3-methyl-ureido)-piperidine-1-carboxylic acid tert.-butyl ester		348
4-[1-(4-Methoxy-phenyl)-3-methyl-ureido]-piperidine-1-carboxylic acid tert.-butyl ester		364
4-(3,3-Dimethyl-1-phenyl-ureido)-piperidine-1-carboxylic acid tert.-butyl ester		348
4-[1-Allyl-3-(4-nitro-benzyl)-ureido]-piperidine-1-carboxylic acid tert.-butyl ester		419

Reaction scheme 1, step 4

3-Methyl-1-phenyl-1-piperidin-4-yl-urea

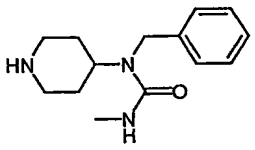
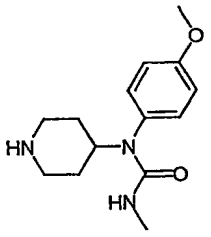
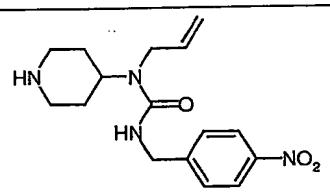
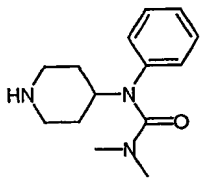


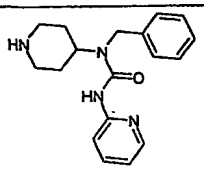
A solution of 4-(3-methyl-1-phenyl-ureido)-piperidine-1-carboxylic acid tert.-butyl ester (15.2g) in dichloromethane (80ml) was treated with trifluoroacetic acid (20ml) and the mixture stirred at ambient temperature for 1 h. The mixture was evaporated and the

residue partioned between 2M aqueous sodium hydoxide solution (100ml) and dichloromethane (200ml). The organic phase was separated, dried (anhydrous magnesium sulphate), filtered and evaporated to give the title compound as a white solid (10.1g, 95%). Mass spectrum 234 $[M+H]^+$.

5

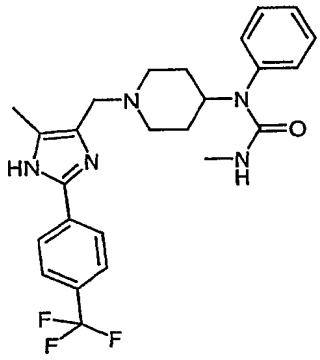
The following compounds were produced in a manner analogous to that described above by replacing the 4-(3-methyl-1-phenyl-ureido)-piperidine-1-carboxylic acid tert.-butyl ester with the appropriate tert-butoxycarbonyl derivative:

Systematic name	Structure	m/z $[M + H]^+$
1-Benzyl-3-methyl-1-piperidin-4-yl-urea		248
1-(4-Methoxy-phenyl)-3-methyl-1-piperidin-4-yl-urea		264
1-Allyl-3-(4-nitro-benzyl)-1-piperidin-4-yl-urea		389
1,1-Dimethyl-3-phenyl-3-piperidin-4-yl-urea		248

1-Benzyl-1-piperidin-4-yl-3-pyridin-2-yl-urea		311

Reaction scheme 1, step 5

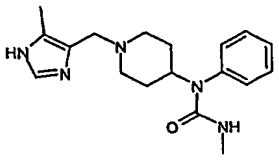
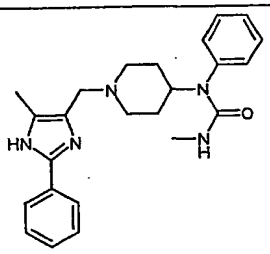
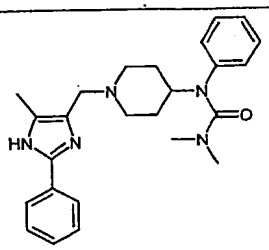
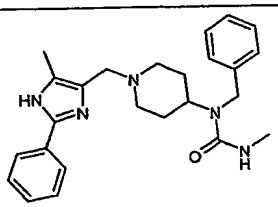
3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-phenyl-urea

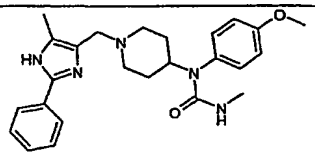
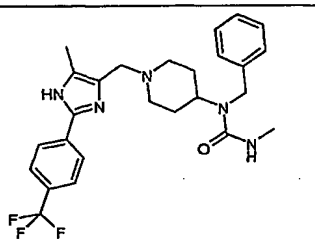
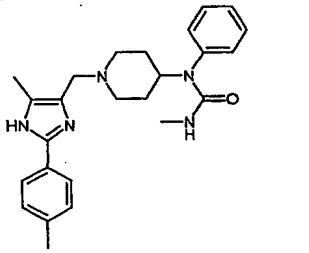
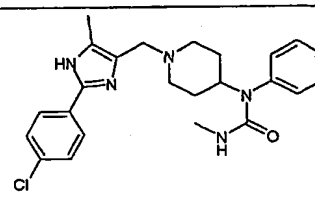
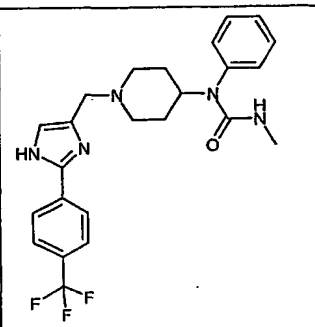


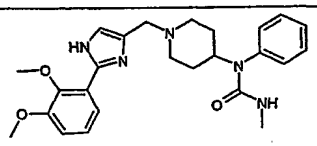
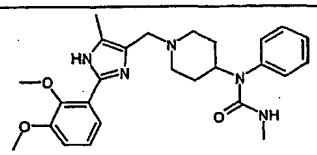
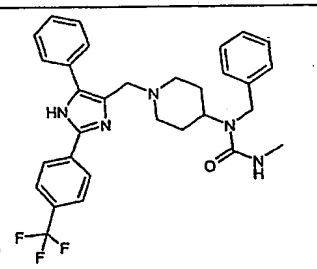
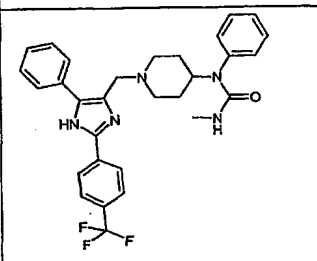
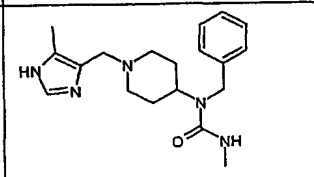
A mixture of 3-methyl-1-phenyl-1-piperidin-4-yl-urea (55mg) and 5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde (60mg) in dichloromethane (10ml) was treated with sodium triacetoxyborohydride (Aldrich 31639-3, 70mg) and stirred at ambient temperature for 2 h. Ethyl acetate (40ml) was added, followed by saturated aqueous sodium hydrogen carbonate (20ml), the organic layer was separated, dried (anhydrous magnesium sulphate), filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with DMAW 240. The resulting acetate salt was partitioned between dichloromethane (10ml) and 2M aqueous sodium hydroxide solution (10ml). The organic phase was separated, dried (anhydrous magnesium sulphate), filtered and evaporated to leave the title compound as a white solid (30mg, 26%). Mass spectrum 472 $[M+H]^+$.

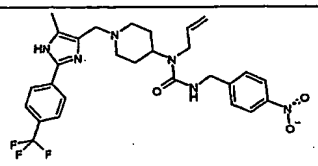
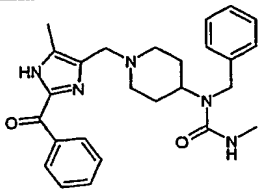
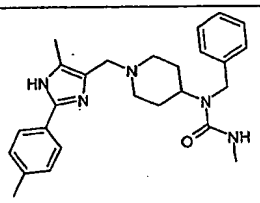
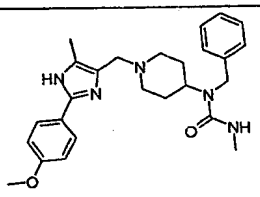
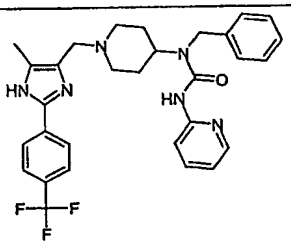
The following compounds were produced in a manner analogous to that described above, by using the appropriate aldehyde prepared as described in reaction schemes 5, 6, 8 or 9 in place of 5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde and

the appropriate amine prepared as described in reaction schemes 1 or 7 in place of 3-methyl-1-phenyl-1-piperidin-4-yl-urea.

Systematic name	Structure	m/z $[M + H]^+$
3-Methyl-1-[1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-phenylurea		328
3-Methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-phenylurea		404
1,1-Dimethyl-3-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-3-phenylurea		418
1-Benzyl-3-methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea		418

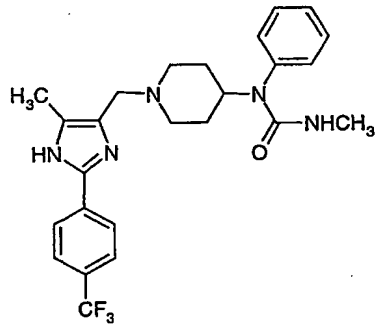
1-(4-Methoxyphenyl)-3-methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea		434
1-Benzyl-3-methyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		486
3-Methyl-1-[1-[[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylurea		418
1-[1-[[2-(4-Chlorophenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea		439
3-Methyl-1-phenyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		458

1-[1-[[2-(2,3-Dimethoxyphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea		450
1-[1-[[2-(2,3-Dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea		464
1-Benzyl-3-methyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		548
3-Methyl-1-phenyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		534
1-Benzyl-3-methyl-1-[1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea		342

1-Allyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-nitrobenzyl)urea		557
1-[1-[(2-Benzoyl-5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-benzyl-3-methylurea		446
1-Benzyl-3-methyl-1-[1-(5-methyl-2-p-tolyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-urea		432
1-Benzyl-1-{1-[2-(4-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea		448
1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-2-yl-urea		549.1

Alternative method of reaction scheme 1 step 5: Alkylation via a chloromethylimidazole intermediate

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea

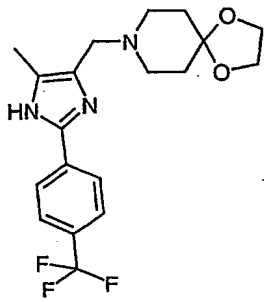


2-[4'-(Trifluromethyl)phenyl]-4-methylimidazole-5-methanol (770mg) was treated cautiously with of thionyl chloride (5ml) and the resulting solution heated at 70°C for 15 min, then cooled and evaporated. The residue was re-evaporated twice with toluene (10ml). The resulting viscous oil was dissolved in dichloromethane (30ml), cooled in an ice/water bath and then treated with 4-(3'-methyl-1'-phenylureido)piperidine (700ml) followed by dropwise treatment with a solution of ethyldiisopropylamine (2ml) in dichloromethane (5ml). After 1 h, the mixture was treated with saturated aqueous sodium hydrogen carbonate solution (30ml). The organic solution was separated, dried (anhydrous magnesium sulfate), filtered and evaporated. The residue was subjected to flash chromatography using a gradient elution [dichloromethane/methanol (97:3) to dichloromethane/methanol/acetic acid/water (240:24:3:2)]. Product-containing fractions were combined and evaporated. The residue was evaporated twice with toluene (20ml) and then dissolved in dichloromethane (40ml). The solution was washed with 2M aqueous sodium hydroxide (40ml), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to about 5ml. Hexane (30ml) was added carefully to precipitate the 1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea as a white solid (330mg, 23%). Mass spectrum 472 $(M+H)^+$.

Examples according to reaction scheme 2:

Reaction scheme 2, step 1

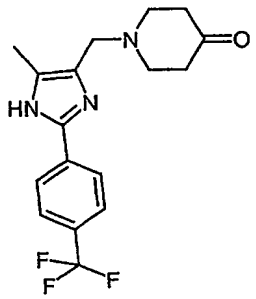
8-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-1,4-dioxa-8-aza-spiro[4.5]decane



A mixture of 5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde (1.6g) and 4-piperidone ethylene ketal (Avocado, 0.9g) in dichloromethane (60ml) was treated with sodium triacetoxyborohydide (Aldrich, 1.86g) and allowed to stir at ambient temperature for 12 h. 2M aqueous sodium hydroxide solution (50ml) was added and the mixture stirred vigorously for 5 min. The organic phase was separated, washed with water (50ml), dried (anhydrous magnesium sulphate), filtered and the solvent removed under reduced pressure. The residue was subject to flash chromatography on silica gel using a gradient elution (dichloromethane/ methanol100:0 to 98:2). This gave the title compound as a white solid (1.21g, 50%). Mass spectrum 382 $[M+H]^+$.

Reaction scheme 2, step 2

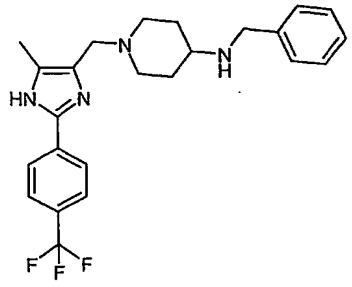
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinone



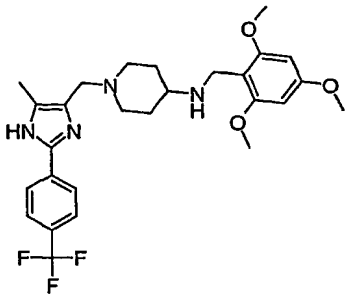
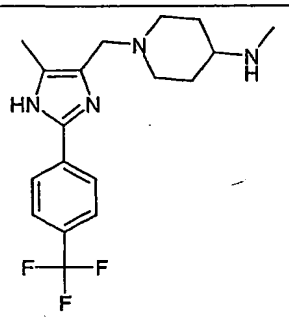
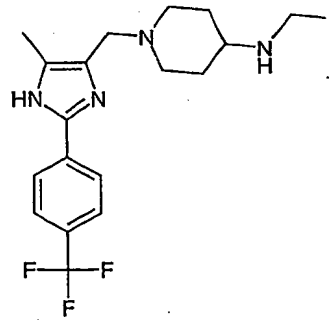
A mixture of 8-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-1,4-dioxa-8-aza-spiro[4.5]decane (16.4g) and 6M hydrochloric acid (200ml) was heated to 90° C for 30 min, cooled and neutralised with 8M aqueous sodium hydroxide solution. The mixture was extracted with dichloromethane (2 x 250ml), and the organic extracts were combined, dried (anhydrous magnesium sulphate), filtered and evaporated. The residue was subjected to flash chromatography on silica gel using a gradient elution (DMAW 240 to DMAW 120) and the resultant acetate salt was partitioned between dichloromethane (100ml) and 2M aqueous sodium hydroxide (75ml).The organic layer was separated, dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure to give the title compound as a white solid (9.65g, 66%). Mass spectrum 438 $[M+H]^+$.

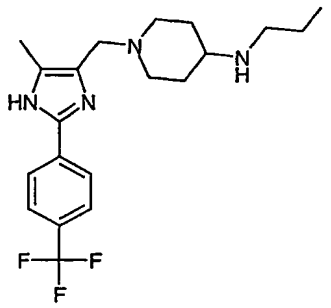
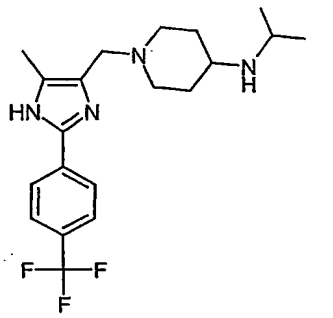
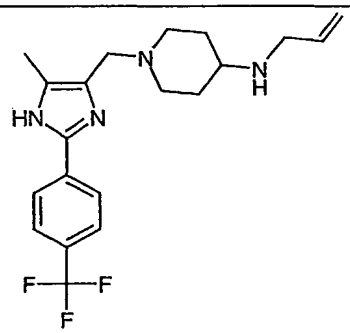
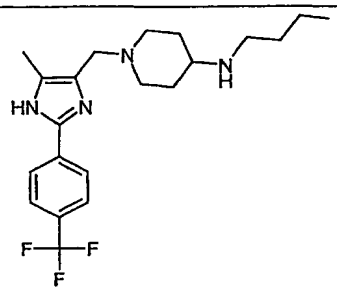
Reaction scheme 2, step 3

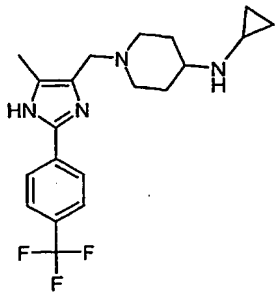
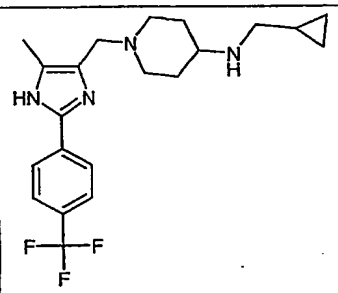
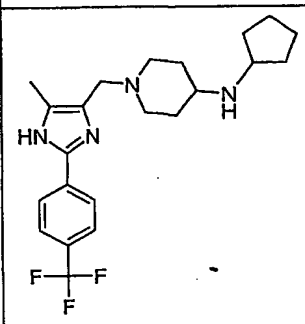
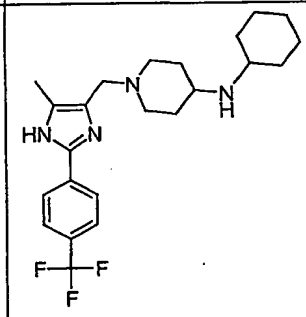
N-Benzyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine

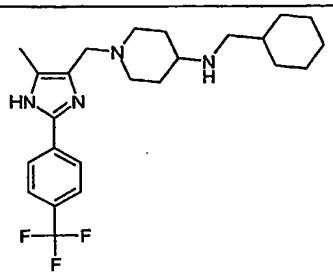
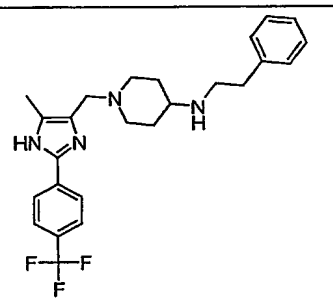
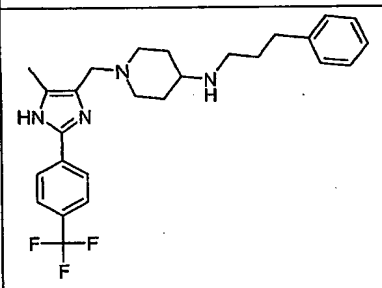
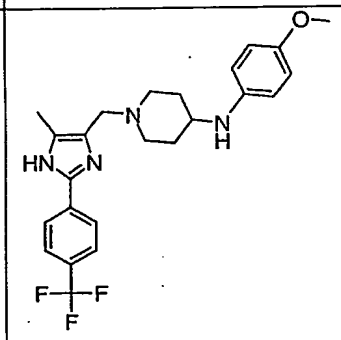


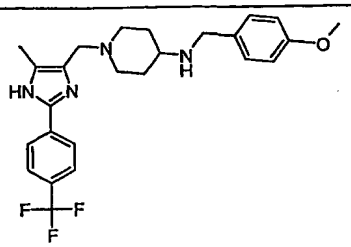
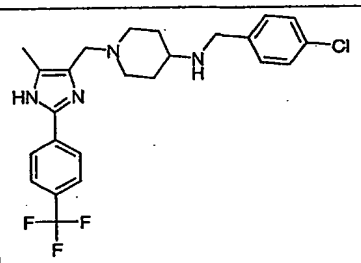
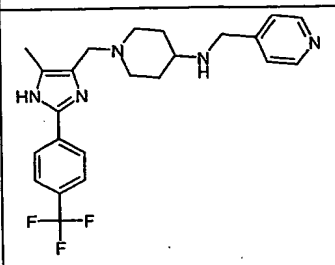
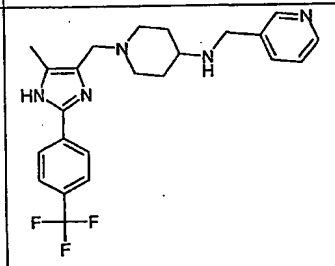
A solution of 1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinone (570mg) in dichloromethane (10ml) was treated with benzylamine (164mg) followed by sodium triacetoxyborohydride (488mg) and a solution of acetic acid (92mg) in dichloromethane (5ml) and stirred at ambient temperature for 1 h. The mixture was diluted with dichloromethane (40ml), washed with 1M aqueous sodium hydroxide solution (10ml), water (2 x 40ml) and brine (30ml). The organic layer was dried (MgSO4), filtered and removed under reduced pressure to give the title compound as a white solid (645mg, 99%). Mass spectrum 429 $[M+H]^+$.

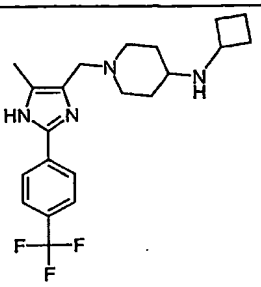
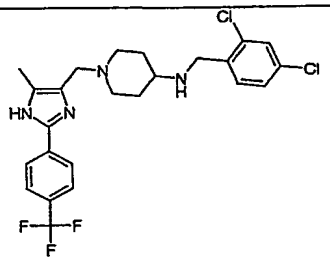
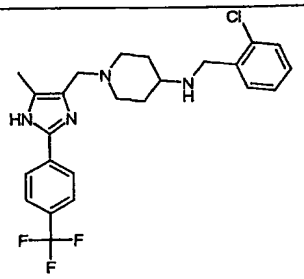
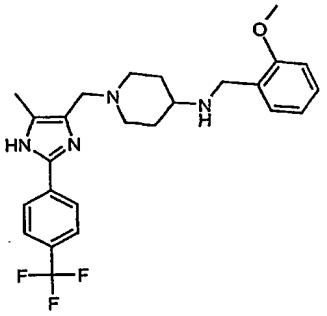
Systematic Name	Structure	m/z $[M + H]^+$
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(2,4,6-trimethoxybenzyl)-4-piperidinamine		519
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-methyl-4-piperidinamine		353
N-Ethyl-1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		367

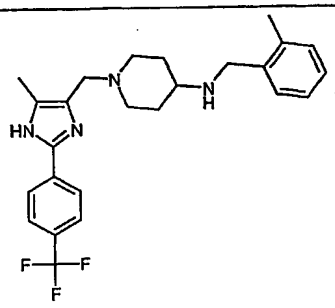
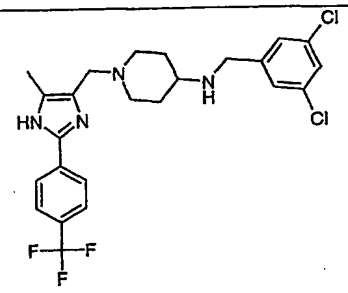
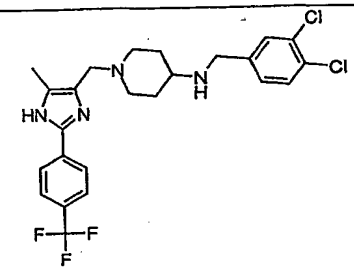
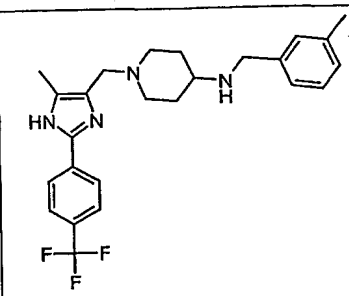
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-propyl-4-piperidinamine		381
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-isopropyl-4-piperidinamine		381
N-Allyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		379
N-Butyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		395

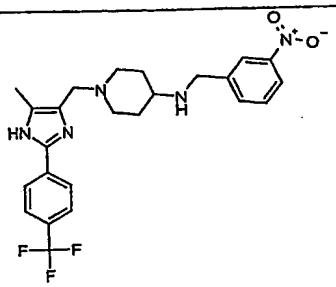
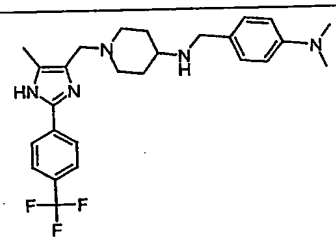
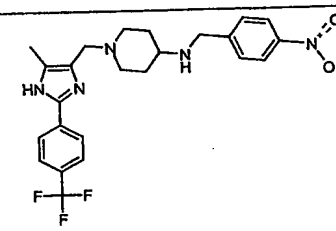
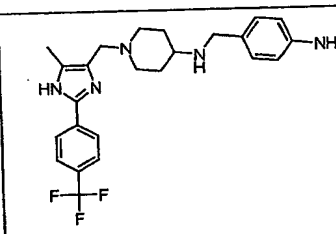
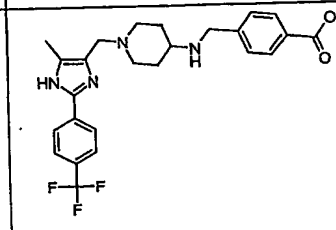
N-Cyclopropyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		379
N-(Cyclopropylmethyl)-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		393
N-Cyclopentyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-piperidinamine		407
N-Cyclohexyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		421

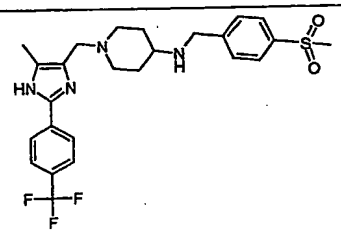
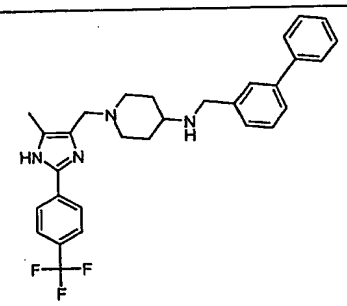
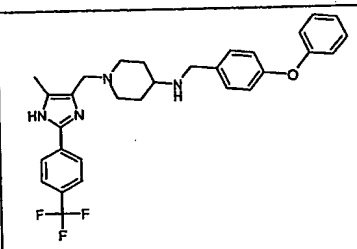
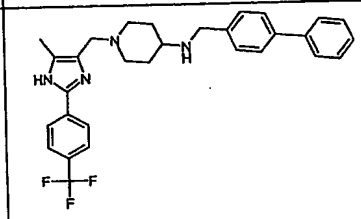
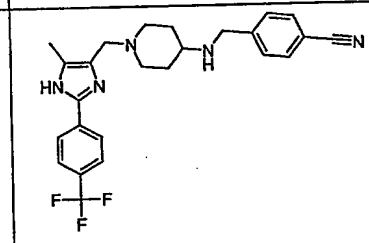
N-(Cyclohexylmethyl)-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		435
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(2-phenylethyl)-4-piperidinamine		443
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(3-phenylpropyl)-4-piperidinamine		457
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(4-methoxyphenyl)-4-piperidinamine		445

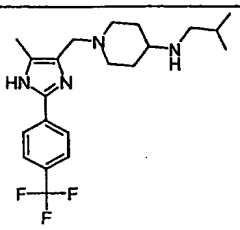
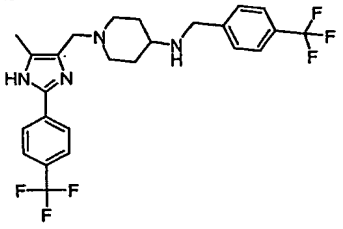
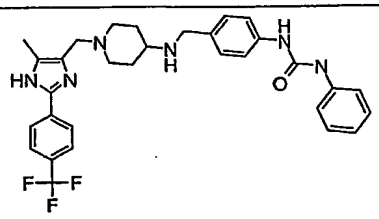
1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(4-methoxybenzyl)-4-piperidinamine		459
N-(4-Chlorobenzyl)-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		464
N-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-4-pyridinemethylamine		430
N-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-pyridinemethylamine		430

N-Cyclobutyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		393
N-(2,4-Dichlorobenzyl)-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		498
N-(2-Chlorobenzyl)-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		464
4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(2-methoxybenzyl)-4-piperidinamine		459

4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(2-methylbenzyl)-4-piperidinamine		443
N-(3,5-Dichlorobenzyl)-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		498
N-(3,4-Dichlorobenzyl)-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		498
4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(3-methylbenzyl)-4-piperidinamine		443

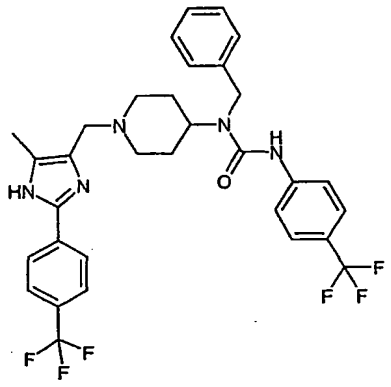
4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(3-nitrobenzyl)-4-piperidinamine		474
4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-[4-(dimethylamino)benzyl]-4-piperidinamine		472
4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(4-nitrobenzyl)-4-piperidinamine		474
N-(4-Aminobenzyl)-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		444
Methyl 4-[[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]aminomethyl]benzoate		487

4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-[4-(methanesulfonyl)benzyl]-4-piperidinamine		507
N-[(3-Biphenylyl)methyl]-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		505
4-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-N-(4-phenoxybenzyl)-4-piperidinamine		521
N-[(4-Biphenylyl)methyl]-4-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine		505
4-[[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]aminomethyl]benzonitrile		454

Isobutyl-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-amine		395
{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-(4-trifluoromethyl-benzyl)-amine		497
1-[4-({1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-ylamino}-methyl)-phenyl]-3-phenyl-urea		563

Reaction scheme 2, step 3.1

1-Benzyl-3-[4-(trifluoromethyl)phenyl]1-[1-[[2-[4-(trifluoromethyl)phenyl-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea

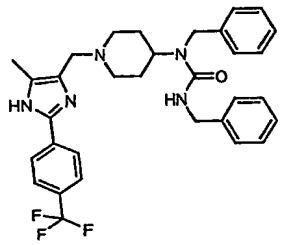


N-Benzyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine (64mg) was dissolved in dichloromethane (1ml) and treated with a solution of 4-(trifluoromethyl)phenyl isocyanate (Lancaster Synthesis 12576, 31mg) in

dichloromethane (1ml). The mixture was stirred at ambient temperature for 18 h and then evaporated. Flash chromatography using a gradient elution [dichloromethane/methanol (95:5) to dichloromethane/methanol (90:10)] afforded, upon evaporation of the product-containing fractions, 1-benzyl-3-[4-(trifluoromethyl)phenyl]1-[1-[[2-[4-(trifluoromethyl)phenyl-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea as a white solid (69mg, 75%) Mass spectrum 616 $(M+H)^+$.

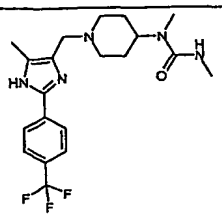
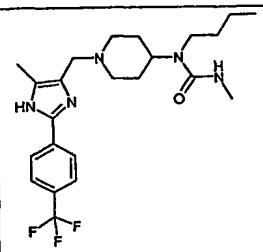
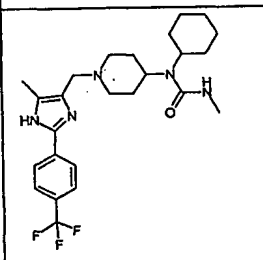
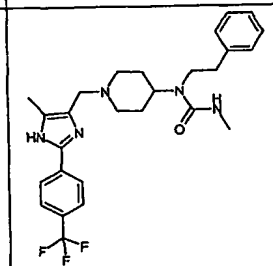
Reaction scheme 2, step 4.1

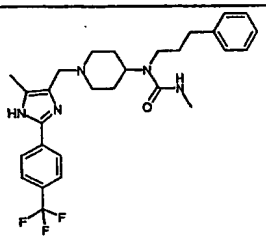
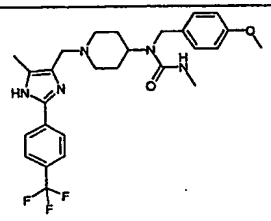
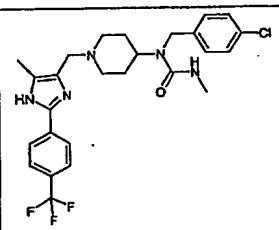
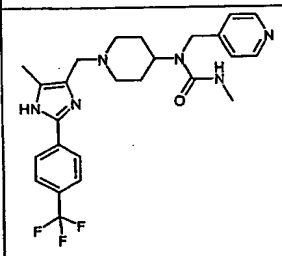
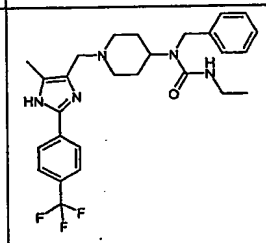
1,3-Dibenzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea

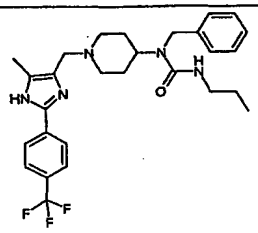
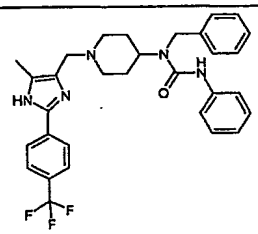
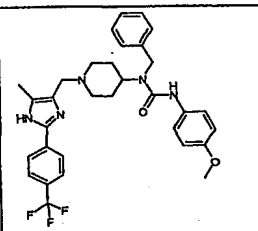
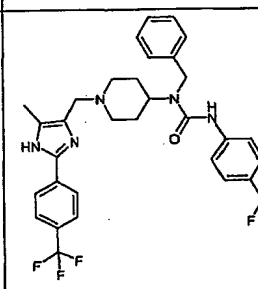
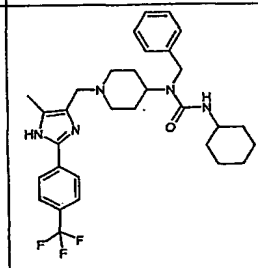


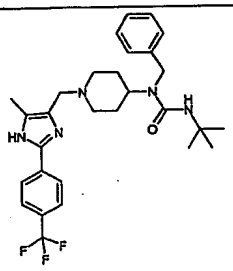
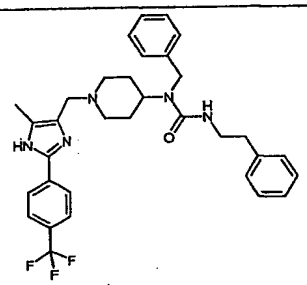
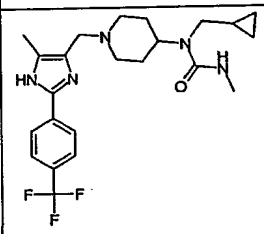
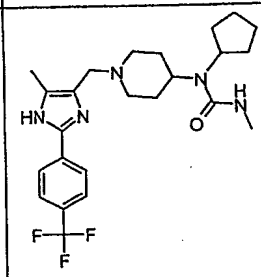
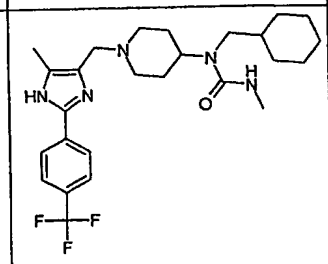
A solution of benzyl-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-amine (64mg) in dichloromethane (1ml) was added to a solution of benzylisocyanate (20mg) in dichloromethane (2ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was loaded directly onto a pre-packed silica gel flash chromatography column and eluted with 20% methanol in dichloromethane. This gave the title compound as a white solid (59mg, 72%). Mass spectrum 548 $[M+H]^+$.

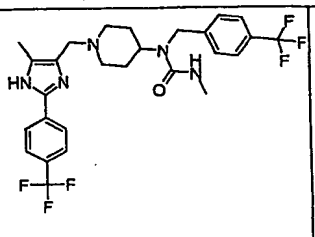
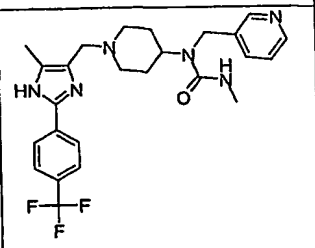
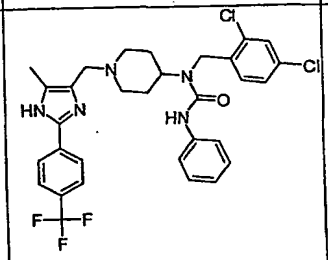
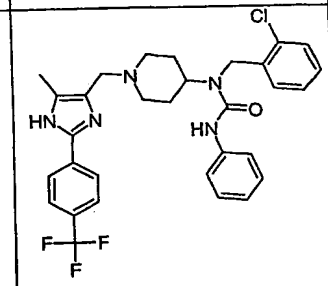
The following compounds were produced in a manner analogous to that described above by using the appropriate isocyanate and the appropriately substituted aminopiperidine:

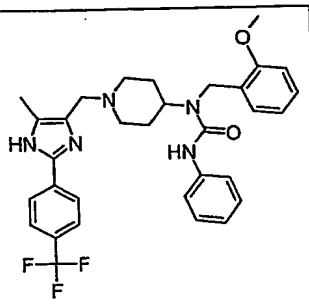
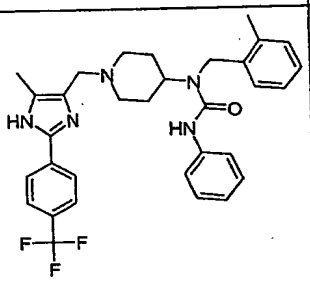
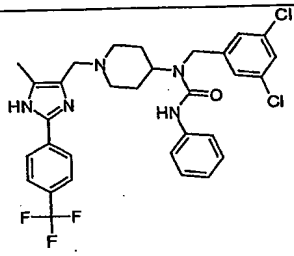
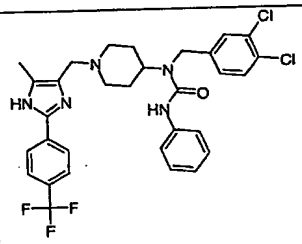
Systematic name	Structure	m/z $[M + H]^+$
1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1,3-dimethylurea		410
1-Butyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea		452
1-Cyclohexyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea		478
1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-(2-phenethyl)urea		500

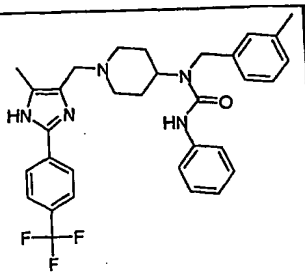
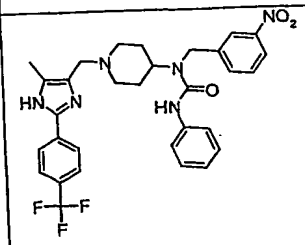
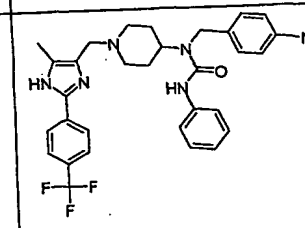
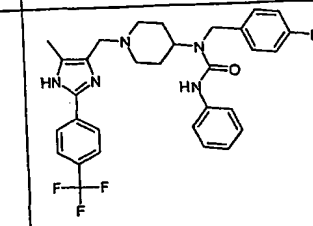
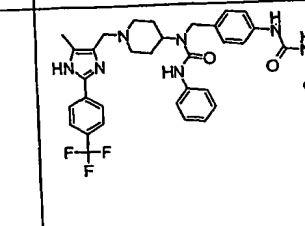
1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-(3-phenylpropyl)urea		514
1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-(4-methoxybenzyl)-3-methylurea		516
1-(4-Chlorobenzyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea		521
1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-[(4-pyridyl)methyl]urea		487
1-Benzyl-3-ethyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		500

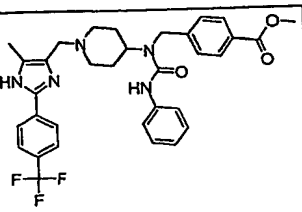
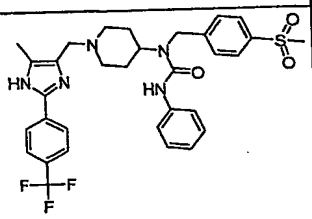
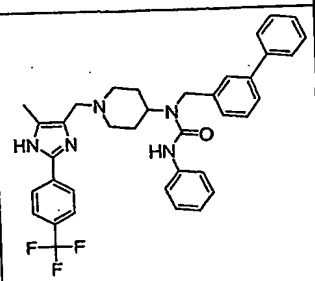
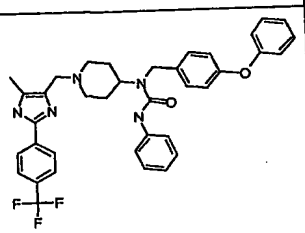
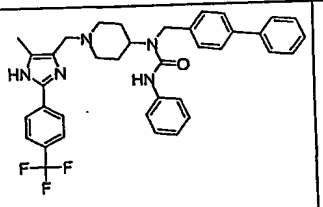
1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-propylurea		514
1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-phenylurea		548
1-Benzyl-1-[1-[[2-[4-trifluoromethyl-phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-methoxyphenyl)urea		578
1-Benzyl-3-[4-(trifluoromethyl)phenyl]1-[1-[[2-[4-(trifluoromethyl)phenyl-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		616
1-Benzyl-3-cyclohexyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		554

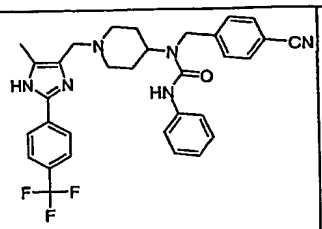
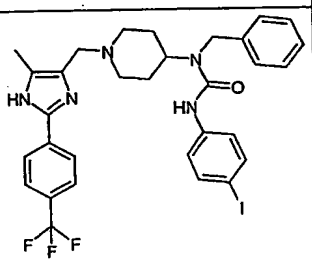
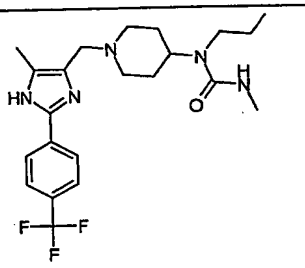
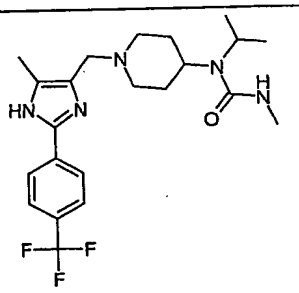
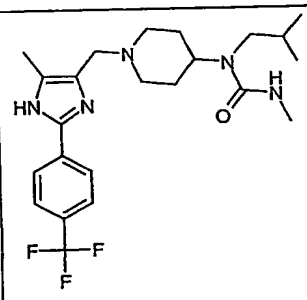
1-Benzyl-3-tert.-butyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea		528
1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(2-phenylethyl)urea		576
1-Cyclopropylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		450.1
1-Cyclopentyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		464.1
1-Cyclohexylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		492.1

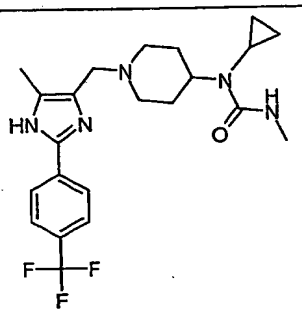
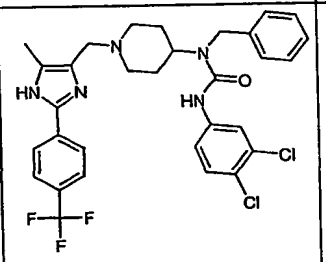
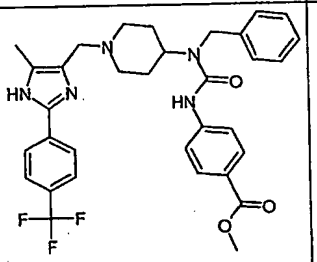
3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-trifluoromethyl-benzyl)-urea		554.2
3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-3-ylmethyl-urea		487.1
1-(2,4-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		616.1
1-(2-Chloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		582.1

1-(2-Methoxy-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		578.2
1-(2-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		562.2
1-(3,5-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		616.1
1-(3,4-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		616.1

1-(3-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		562.2
1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(3-nitro-benzyl)-3-phenyl-urea		593.1
1-(4-Dimethylamino-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		591.2
1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-nitro-benzyl)-3-phenyl-urea		593.1
1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-1-[4-(3-phenyl-ureido)-benzyl]-urea		682.2

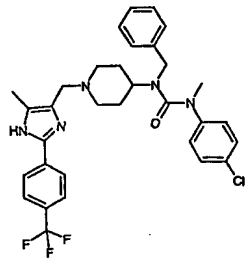
4-(1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-ureidomethyl)-benzoic acid methyl ester		606.2
1-(4-Methanesulfonyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		626.1
1-Biphenyl-3-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		624.2
RO-33-8371/000		640.2
1-Biphenyl-4-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		624.2

1-(4-Cyano-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		573.2
1-Benzyl-3-(4-iodo-phenyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		674.0
3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-propyl-urea		438.1
1-Isopropyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		438.1
1-Isobutyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		452.1

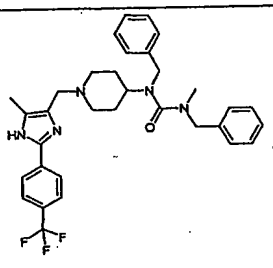
1-Cyclopropyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		436.1
1-Benzyl-3-(3,4-dichloro-phenyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		616.0
4-(3-Benzyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-ureido)-benzoic acid methyl ester		606.1

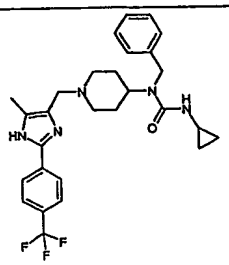
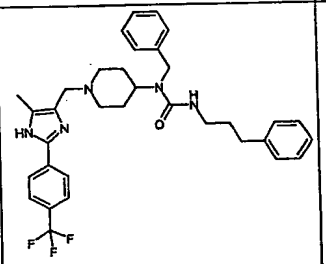
Reaction scheme 2, step 4.4

1-Benzyl-3-(4-chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea



A solution of p-chloro-N-methylbenzylamine (282mg) in dichloromethane (10ml) was treated with pyridine (0.96ml) followed by a solution of 20% phosgene in toluene (3.1ml) and stirred at ambient temperature for 16 h. The mixture was quenched by the addition of saturated sodium hydrogen carbonate (10ml), and the organic layer was then separated, dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure. The residue was dissolved in dichloromethane (10ml) and a solution of N-benzyl-1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinamine (657mg) in dichloromethane (10ml) was added followed by more pyridine (0.96ml) and the mixture stirred for a further 16 h. The mixture was diluted with dichloromethane (40ml) followed by brine (2 x 20ml). The organic layer wasseparated, dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified by flash chromotography eluting with 10% methanol in dichloromethane to give the title compound (512mg, 56%). Mass spectrum 597 $[M+H]^+$.

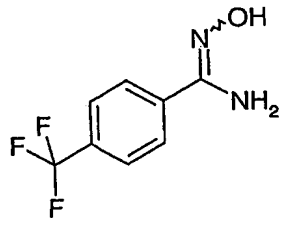
Systematic name	Structure	m/z [M + H]+
1,3-Dibenzyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		576

1-Benzyl-3-cyclopropyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		512
1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3-phenylpropyl)urea		590

Examples according to reaction scheme 3:

Reaction scheme 3, step 1

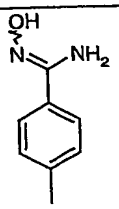
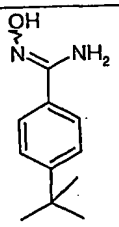
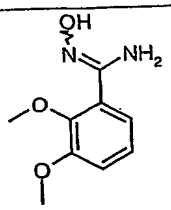
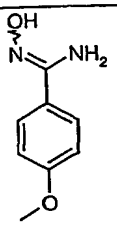
4-Trifluoromethylphenyl-amidoxime

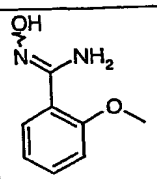
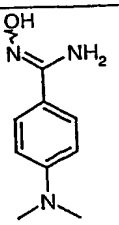
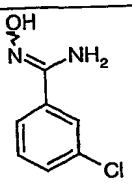
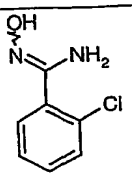


A solution of 4-trifluoromethyl benzonitrile (Avocado 14514, 15g) in toluene (200ml) was treated with methanol (15ml) followed by hydroxylamine hydrochloride (2.25g) and potassium tert-butoxide (3.52g). The mixture was heated to 80°C and treated with further portions of hydroxylamine hydrochloride (1.07g) and potassium tert-butoxide (3.52g) after 2, 4 and 6 h. The mixture was stirred for 16 h, and then cooled. The solvents were evaporated and the residue partitioned between water (100ml) and dichloromethane (200ml). The aqueous layer was extracted with two further portions of

dichloromethane (2 x 200ml). The organic solutions were combined, dried (anhydrous magnesium sulphate), filtered and evaporated to give the title compound as a white solid (16.7g, 93%). Mass spectrum, 215 $[M+H]^+$.

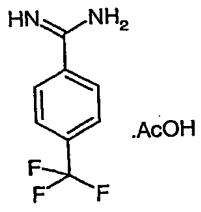
The following compounds were produced in a manner analogous to that described above by using the appropriately substituted benzonitrile in place of 4-trifluoromethyl benzonitrile:

Systematic name	Structure	m/z $[M + H]^+$
N-Hydroxy-4-methyl-benzamidine		151
4-tert.-butyl-N-hydroxy-benzamidine		193
N-Hydroxy-2,3-dimethoxy-benzamidine		197
N-Hydroxy-4-methoxy-benzamidine		167

N-Hydroxy-2-methoxy-benzamidine		167
4-Dimethylamino-N-hydroxy-benzamidine		151
3-Chloro-N-hydroxy-benzamidine		171
2-Chloro-N-hydroxy-benzamidine		171

Reaction scheme 3, step 2

4-Trifluoromethylphenyl amidine acetate

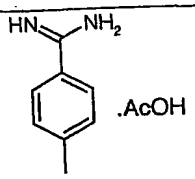
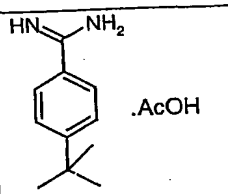
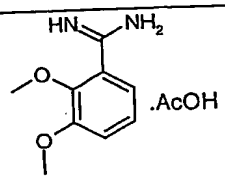
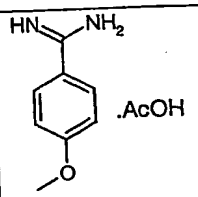


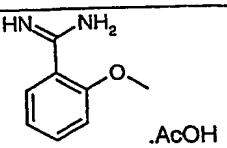
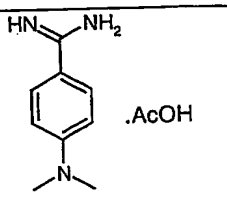
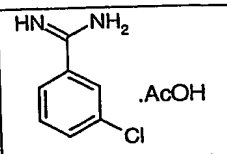
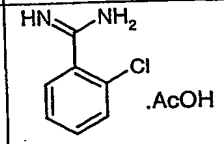
A solution of 4-trifluoromethyl amidoxime (16.7g) in acetic acid (400ml) was treated with acetic anhydride (11.6ml). After 15 min, 10% palladium on charcoal (Fluka, 2.5g) was

added and the mixture was shaken under an atmosphere of hydrogen for 2 h. The mixture was filtered through Hyflo, evaporated, and then azeotroped twice with toluene. The resulting white solid was triturated with hexane to yield the title compound as a white solid (19.1g, 94%). Mass spectrum 189 $[M+H]^+$.

5

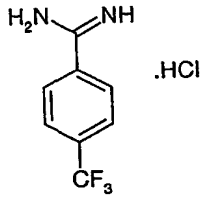
The following compounds were produced in a manner analogous to that described above by replacing the 4-trifluoromethyl amidoxime with the appropriate amidoxime:

Systematic name	Structure	m/z $[M + H]^+$
4-Methyl-benzamidine acetate		135
4-tertButyl-benzamidine acetate		177
2,3-Dimethoxy-benzamidine acetate		181
4-Methoxy-benzamidine acetate		151

2-Methoxy-benzamidine acetate		151
4-Dimethylamino-benzamidine acetate		135
3-Chloro-benzamidine acetate		155
2-Chloro-benzamidine acetate		155

Example from reaction scheme 4 of the process:

4-(Trifluoromethyl)benzamidine hydrochloride



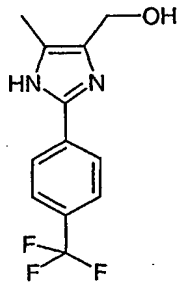
A solution of 4-(trifluoromethyl)benzonitrile (Avocado 14514, 15g) in anhydrous methanol (90ml) was treated with sodium methoxide (0.50g) and the resulting solution stirred for 4 d at ambient temperature. After this time, ammonium chloride (4.7g) was added and the mixture stirred for a further day. The mixture was subsequently evaporated and the residual white solid triturated in diethyl ether, filtered and dried to afford of 4-

(trifluoromethyl)benzamidine hydrochloride as a white solid (14.2g, 72%). Mass spectrum 188 $[M]^+$.

Examples according to reaction scheme 5:

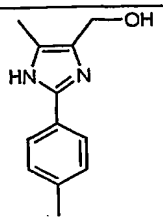
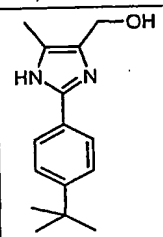
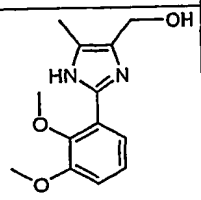
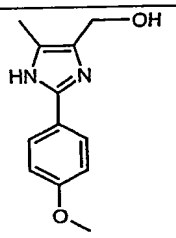
Reaction scheme 5, step 1

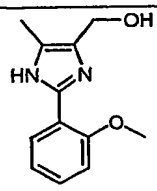
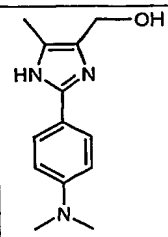
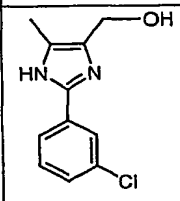
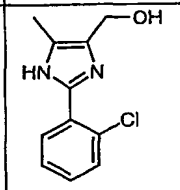
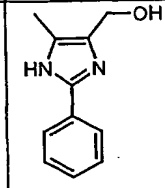
[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol



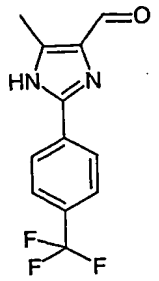
A suspension of 4-trifluoromethyl benzamidine acetate (20g) and 2, 3-butanedione (8g) in water (40ml) was treated with 2M aqueous sodium hydroxide solution until pH8 was reached. The mixture was cooled in an ice bath and stirred for 2 h, the resultant solid was then collected by filtration and washed with water. The wet solid was treated with 4M aqueous hydrochloric acid (150ml) and heated under reflux for 4 h then cooled in an ice bath and the pH adjusted to pH9 with 8M aqueous sodium hydroxide solution. The resultant solid was collected by filtration, washed sequentially with water and 50% aqueous ethanol and dried to give the title compound as a white solid (16.9g, 82%). Mass spectrum 257 $[M+H]^+$.

The following compounds were produced in a manner analogous to that described above by using the appropriate amidine acetate or hydrochloride prepared as described in reaction scheme 3 or reaction scheme 4 in place of the 4-trifluoromethyl benzamidine acetate

Systematic name	Structure	m/z $[M + H]^+$
(5-Methyl-2-p-tolyl-1H-imidazol-4-yl)-methanol		203
[2-(4-tert.-butyl-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		245
[2-(2,3-Dimethoxy-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		249
[2-(4-Methoxy-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		219

[2-(2-Methoxy-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		219
[2-(4-Dimethylamino-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		232
[2-(3-Chloro-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		223
[2-(2-Chloro-phenyl)-5-methyl-1H-imidazol-4-yl]-methanol		223
(5-Methyl-2-phenyl-1H-imidazol-4-yl)-methanol		189

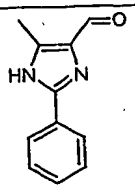
Reaction scheme 5, step 2.1

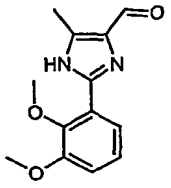


5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde

A mixture of [5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol (1.2g) and manganese dioxide (4g) in 1, 4-dioxane (50ml) was heated at reflux for 1.5 h. The hot mixture was filtered through Hyflo and the filtered solids washed with hot 1, 4-dioxane. The solvent was removed under reduced pressure and the residue was recrystallized from cyclohexane/ethyl acetate to yield the title compound as a pale yellow solid (0.6g, 50%). Mass spectrum 255 $[M+H]^+$.

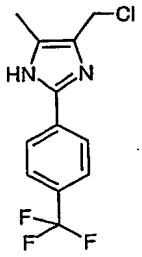
The following compounds were synthesised in a manner analogous to that described above by using the appropriate hydroxymethyl imidazole, prepared as described in reaction scheme 5, step 1, in place of the [5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol:

Systematic name	Structure	m/z [M + H]+
5-Methyl-2-phenyl-1H-imidazole-4-carbaldehyde		187

2-(2,3-Dimethoxy-phenyl)-5-methyl-1H-imidazole-4-carbaldehyde		247

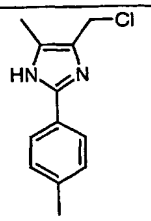
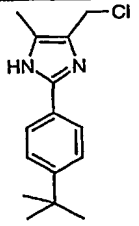
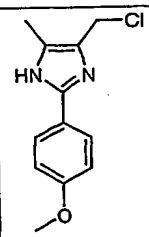
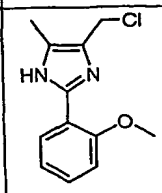
Reaction scheme 5, step 2.2

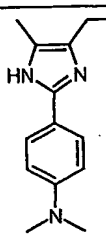
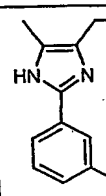
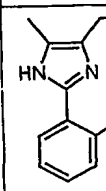
4-Chloromethyl-5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole



[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol (20g) was treated with thionyl chloride (250ml) and heated at 85°C for 20 min. The thionyl chloride was removed under reduced pressure and the residue azeotroped twice with toluene to give the title compound as a pale yellow solid (14.5g, 68%). Mass spectrum 274 $[M+H]^+$.

The following compounds were synthesised in a manner analogous to that described above by using the appropriate hydroxymethyl imidazole, prepared as described in reaction scheme 5, step 1, in place of the [5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol:

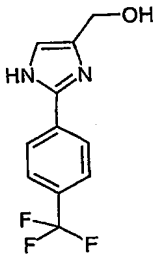
Systematic Name	Structure	m/z $[M + H]^+$
4-Chloromethyl-5-methyl-2-p-tolyl-1H-imidazole		221
2-(4-tert.-butyl-phenyl)-4-chloromethyl-5-methyl-1H-imidazole		263
4-Chloromethyl-2-(4-methoxy-phenyl)-5-methyl-1H-imidazole		237
4-Chloromethyl-2-(2-methoxy-phenyl)-5-methyl-1H-imidazole		237

[4-(4-Chloromethyl-5-methyl-1H-imidazol-2-yl)-phenyl]-dimethyl-amine		250
4-Chloromethyl-2-(3-chloro-phenyl)-5-methyl-1H-imidazole		242
4-Chloromethyl-2-(2-chloro-phenyl)-5-methyl-1H-imidazole		242

Examples according to reaction scheme 6

Reaction scheme 6, step 1

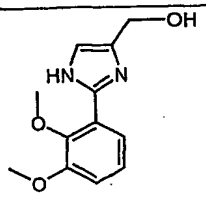
[2-(4-Trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol



A mixture of 4-trifluoromethylbenzamidine hydrochloride (2.5g) and 1, 3-dihydroxyacetone dimer (Avocado 14189, 2g) was heated at 80°C in concentrated ammonia solution (20ml) for 1 h. The mixture was allowed to cool and the product

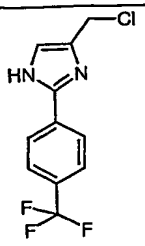
extracted with ethyl acetate (150ml). The organic phase was dried (anhydrous magnesium sulphate), filtered and evaporated. The residue was triturated in diethyl ether to give the title compound as a white solid (1.2g, 44%). Mass spectrum 243 $[M+H]^+$.

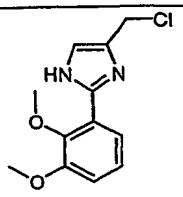
The following compounds were synthesised using a method analogous to that described above by using the appropriate amidine hydrochloride, prepared as described in reaction scheme 4 or the amidine acetate prepared as described in reaction scheme 3, in place of the 4-trifluoromethylbenzamidine hydrochloride

Systematic name	Structure	m/z $[M + H]^+$
[2-(2,3-Dimethoxy-phenyl)-1H-imidazol-4-yl]-methanol		235

Reaction scheme 6, step 2.2

The following compounds were produced in a manner analogous to that described in reaction scheme 5, step 2.2 by using the appropriate hydroxymethyl imidazole, prepared as described in reaction scheme 6, step1, in place of the [5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-yl]-methanol:

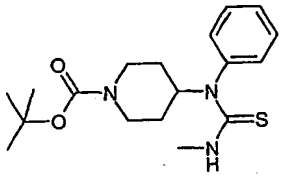
Systematic name	Structure	m/z $[M + H]^+$
4-Chloromethyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole		261

4-Chloromethyl-2-(2,3-dimethoxy-phenyl)-1H-imidazole		253

Examples according to reaction scheme 7:

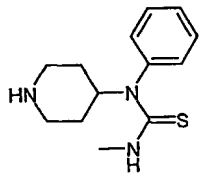
Reaction scheme 7, step 1

4-(3-Methyl-1-phenyl-thioureido)-piperidine-1-carboxylic acid tert.-butyl ester



A solution of 4-phenylamino-piperidine-1-carboxylic acid tert.-butyl ester (0.4g) in a mixture of ethanol (10ml) and toluene (10ml) was treated with methylisothiocyanate (Aldrich 11277-1, 0.11g) and heated to 80°C for 2 h. The solvents were removed under reduced pressure and the residue was triturated with hexane to give the title compound as a white solid (0.27g, 53%). Mass spectrum 340 $[M+H]^+$.

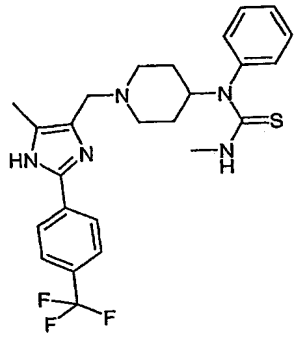
4-(3-Methyl-1-phenyl-thioureido)-piperidine



A solution of 4-(3-methyl-1-phenyl-thioureido)-piperidine-1-carboxylic acid tert.-butyl ester (200mg) in dichloromethane (10ml) was treated with trifluoroacetic acid (3ml) and stirred at ambient temperature overnight. The solvents were evaporated and the

residue partitioned between dichloromethane (50ml) and aqueous sodium hydroxide solution (1M, 40ml). The organic layer was separated, dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure to give the title compound as a white solid (80mg, 56%). Mass spectrum 250 $[M+H]^+$.

3-Methyl-1-[1-[[5-methyl-2-[4(trifluoromethyl)phenyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylthiourea

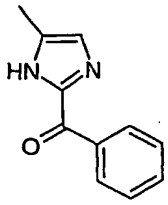


To a mixture of 4-(3-methyl-1-phenyl-thioureido)-piperidine (60mg) and 5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde (65mg) in dichloromethane (10ml) was added sodium triacetoxy borohydride (75mg) followed by acetic acid (2 drops) and the mixture stirred at ambient temperature for 4 h. Dichloromethane (50ml) was added and the mixture washed with 1M aqueous sodium hydroxide solution (50ml) followed by brine (50ml). The organic layer was dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with 2% methanol in dichloromethane to give the title compound as a white solid (30mg, 26%). Mass spectrum 488 $[M+H]^+$.

Examples according to reaction scheme 8:

Reaction scheme 8, step 1

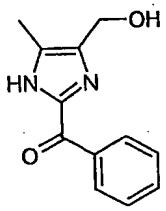
(5-Methyl-1H-imidazol-2-yl)-phenyl-methanone



Benzoyl chloride (17g) was added dropwise to a stirred solution of 4-methylimidazole (Aldrich 19988-5, 5g) in a mixture of pyridine (5ml) and triethylamine (17ml) under an atmosphere of nitrogen and stirring continued for 2 h (mechanical stirring required). 7.5M Aqueous sodium hydroxide solution (6ml) was added and the mixture heated under reflux for 40 min. The mixture was allowed to cool and diluted with water (40ml). The resultant precipitate was collected by filtration, washed with water, dried and recrystallized from toluene to give the title compound as a white solid (1.7g, 15%). Mass spectrum 187 $[M+H]^+$.

Reaction scheme 8, step 2

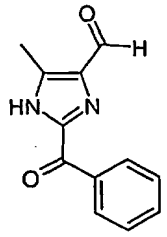
(5-Methyl-1H-imidazol-2-yl)-phenyl-methanol



A mixture of 5-methyl-1H-imidazol-2-yl)-phenyl-methanone (1g), 36% w/w formaldehyde in water (6.4ml), 2M aqueous sodium hydroxide (2ml), ethanol (30ml) and water (15ml) was heated at 55°C for 48 h. The volatile organics were removed under reduced pressure and the residue partitioned between dichloromethane (30ml) and a further portion of water (10ml). The aqueous layer was re-extracted with dichloromethane (2 x 20ml). The combined organic solutions were dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure. Flash chromatography eluting with 5% methanol in dichloromethane gave the title compound as white solid (0.69g, 60%). Mass spectrum 217 $[M+H]^+$.

Reaction scheme 8, step 3

2-Benzoyl-5-methyl-1H-imidazole-4-carbaldehyde

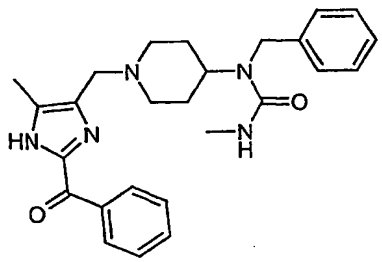


A solution of (5-methyl-1H-imidazol-2-yl)-phenyl-methanol in dichloromethane (25ml) and 1, 4-dioxane (25ml) was treated with manganese dioxide (2.6g) and heated at 80° C for 1 h. The mixture was filtered through celite and the organic solution was dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure to give the title compound as a white solid (308mg, 48%). Mass spectrum 215 $[M+H]^+$.

Reaction scheme 8, step 4

This reaction is carried out in a manner analogous to that described in reaction scheme 1 step 5 .

1-[1-[(2-Benzoyl-5-methyl-1H-imidazol-4-yl)]methyl]-4-piperidinyl]-1-benzyl-3-methylurea

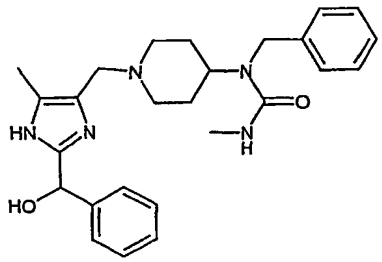


To a mixture of 2-benzoyl-5-methyl-1H-imidazole-4-carboxaldehyde (300mg) and 1-benzyl-3-methyl-1-piperidin-yl-urea (350mg) in dichloromethane (25ml) was added sodium triacetoxy borohydride (420mg) and the mixture stirred at ambient temperature for 3 h. The mixture was washed with aqueous sodium hydroxide solution (1M, 20ml), and brine (2x20ml), dried (anhydrous magnesium sulphate), filtered and the solvents

removed under reduced pressure. The residue was purified by flash chromotography eluting with 4% methanol in dichloromethane to give the title compound as white solid (405mg, 65%). Mass spectrum 446 $[M+H]^+$.

Reaction scheme 8, step 5

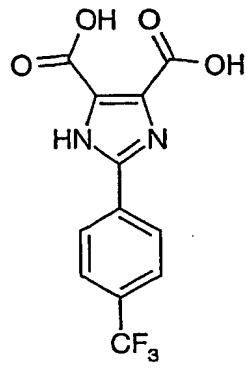
1-Benzyl-1-[1-[[2-[(RS)-(hydroxy)(phenyl)methyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea



To a solution of 1-benzyl-1-{1-[2-(hydroxy-phenyl-methyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea (0.06g) in isopropyl alcohol (8ml) was added sodium borohydride (0.03g) and the mixture stirred at ambient temperature for 1 h. The mixture was then treated with saturated sodium chloride solution (20ml) and extracted with ethyl acetate (2 x 20ml). The combined organic solutions were dried (anhydrous magnesium sulphate), filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with DMAW 240. The resultant acetate salt was partitioned between dichloromethane (100ml) and 2M aqueous sodium hydroxide (10ml). The organic phase was separated, dried (anhydrous magnesium sulphate), filtered and evaporated to give the title compound as a white solid (33mg, 54%). Mass spectrum 448 $[M+H]^+$.

Reaction scheme 9, step 1

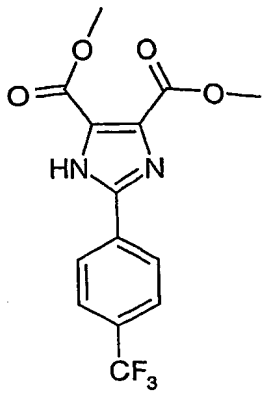
Methyl 2-[4-(trifluoromethyl)phenyl]-imidazole-4,5-dicarboxylate



To d-tartaric acid (6.0g) was added concentrated nitric acid (70%, 7ml) followed cautiously by fuming nitric acid (100%, 17ml). Concentrated sulfuric acid (26ml) was added dropwise ensuring the temperature was kept between 30°C and 40°C by the judicious use of an ice/water bath to cool the mixture as required. Upon addition, the mixture was cooled to 0°C using an ice/water bath. The precipitated solid was filtered off and dried. The dried solid was added to crushed ice (100g), the mixture cooled to –10°C and neutralised by the addition of concentrated aqueous ammonia. A further 12ml of concentrated aqueous ammonia was added followed by 4-(trifluoromethyl)benzaldehyde (Avocado 15276, 6.96g). The mixture was stirred at 0°C for 6 h then for 18 h at ambient temperature. The mixture was neutralised with concentrated hydrochloric acid and the precipitated product was filtered, washed with water and dried to give 2-[4-(trifluoromethyl)phenyl]imidazole-4,5-dicarboxylic acid a white solid. (740mg, 6%). ^{1}H NMR (400MHz,DMSO-d_6): δ[ppm] 7.89 (2H, d), 8.36 (2H, d); Mass spectrum 342 $[M+H+CH_3CN]^+$.

Reaction scheme 9, step 2

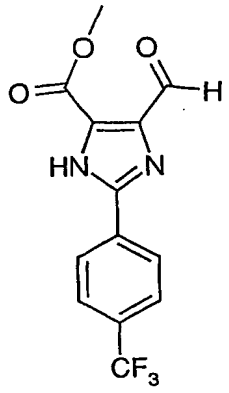
Dimethyl 2-[4-(trifluoromethyl)phenyl]imidazole-4,5-dicarboxylate



A solution of 2-[4-(trifluoromethyl)phenyl]imidazole-4,5-dicarboxylic acid (600mg) in methanol (30ml) was treated with concentrated sulfuric acid (0.5ml) and the mixture heated at reflux for 5 h then cooled and allowed to stand for 18 h. The solvent was evaporated and the residue partitioned between ethyl acetate (20ml) and saturated aqueous sodium hydrogen carbonate solution (20ml). The organic phase was separated, dried (anhydrous magnesium sulfate), filtered and evaporated to give dimethyl 2-[4-(trifluoromethyl)phenyl]imidazole-4,5-dicarboxylate as a white solid (320mg, 49%). Mass spectrum 329 $[M+H]^+$.

Reaction scheme 9, step 3

Methyl 2-[4-(trifluoromethyl)phenyl]-4-formylimidazole-5-carboxylate



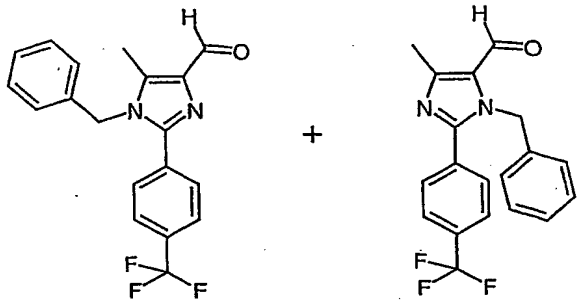
A solution of dimethyl 2-[4-(trifluoromethyl)phenyl]imidazole-4,5-dicarboxylate (300mg) in tetrahydrofuran (20ml) was treated cautiously with 60% w/w sodium hydride (44mg) and the mixture heated at 60°C for 5 min. The mixture was then cooled to –70°C using a dry ice/acetone bath and treated dropwise with 1M diisobutylaluminium hydride

in dichloromethane (1.1ml). After 1.5 h, a further 1.1ml of diisobutylaluminium hydride solution was added dropwise. After a further 2 h, the reaction mixture was treated cautiously with 50% v/v aqueous acetic acid (2ml) and then allowedto warm to ambient temperature. The mixture was evaporated and the residue partitioned between ethyl acetate (20ml) and saturated aqueous sodium hydrogen carbonate solution (20ml). The organic phase was separated, dried (anhydrous magnesium sulfate), filtered and evaporated. The product was purified by flash chromatography using diethyl ether/isohexane (2:1)as eluant to give methyl 2-[4-(trifluoromethyl)phenyl]-4-formylimidazole-5-carboxylateas a white solid(40mg, 15%). Mass spectrum 299 $[M+H]^+$.

Examples according to reaction scheme 10:

Reaction scheme 10, step 1

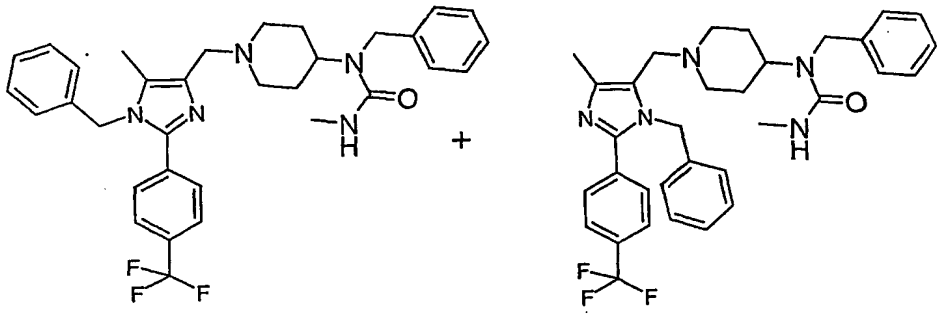
1-Benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde and 3-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carbaldehyde



To a suspension of 60% w/w sodium hydride (47mg) in dimethyl formamide (10ml) was added a solution of 5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde (250mg) in dimethyl formamide (2ml) and the mixture stirred at ambient temperature for 45 min. Benzyl bromide (16µl) was added and stirring continued for a further 2 h. The dimethyl formamide was removed under reduced pressure and the residue partitioned between ethyl acetate (50ml) and water. The organic solution wasseparated, dried (anhydrous sodium sulphate), filtered and evaporated under reduced pressure to give the title compounds as a 1:1 mixture (280mg, 84%). This mixture was used directly in the next step. Mass spectrum 345 $[M+H]^+$

Reaction scheme 10, step 2

1-Benzyl-1-{1-[1-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea and 1-benzyl-1-{1-[3-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea

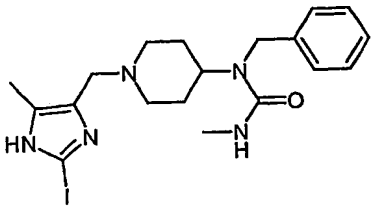


To a mixture of 1-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazole-4-carbaldehyde and 3-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carbaldehyde (80mg) in dichloromethane (10ml) was added 1-benzyl-3-methyl-1-piperidin-4-yl-urea (57mg) followed by sodium triacetoxyborohydride (80mg) and the mixture was stirred at ambient temperature for 16 h. Saturated aqueous sodium hydrogen carbonate solution (10ml) was added, the organic layer was then separated, dried (anhydrous sodium sulpahate), filtered and concentrated under reduced pressure. The residue was purified using a preparative liquid chromatography-mass spectroscopy system with a YMC-ODSA C-18 reverse phase column, using a gradient elution over 15 min. At t = 0 min A = 95%, B = 5%, at t = 15 min A = 5%, B = 95% (A = water/0.1% formic acid B = 90% methanol/10% water/0.1% formic acid. This gave 1-benzyl-1-{1-[3-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea (Rt = 4.08 min, 9mg, 7%) and 1-benzyl-1-{1-[1-benzyl-5-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea (Rt = 6.60 min, 14mg, 11%), both as white solids. Mass spectrum 577 $[M+H]^+$.

Examples according to reaction scheme 11:

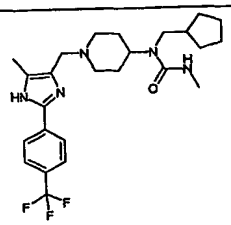
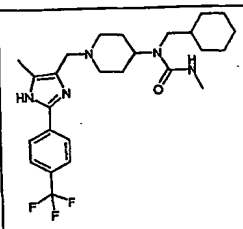
Reaction scheme 11, step 1

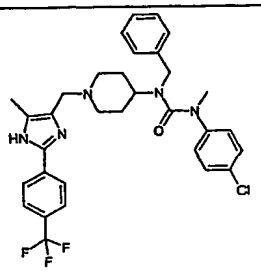
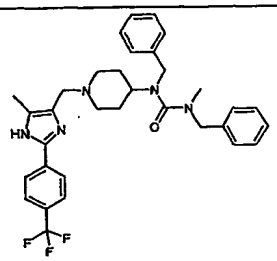
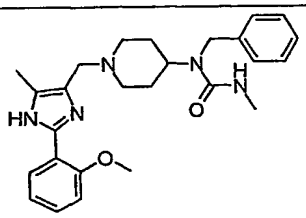
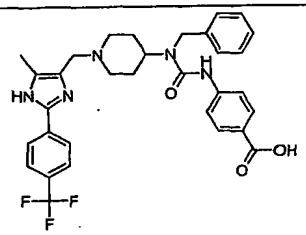
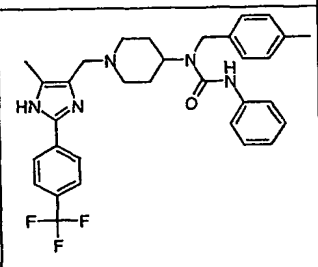
1-Benzyl-1-[1-(2-iodo-5-methyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-3-methyl-urea

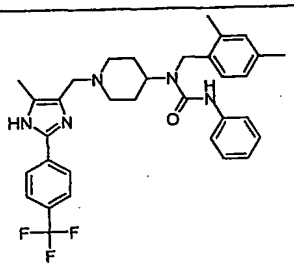


A solution of 1-benzyl-3-methyl-1-[1-(5-methyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-urea (200mg) in a mixture of dichloromethane (20ml) and water (20ml) was treated dropwise with a solution of iodine (150mg) in dichloromethane (10ml) and stirred at ambient temperature for 15 min. The pH of the mixture was adjusted to 9 by the addition of 2M aqueous sodium hydroxide solution and stirring was continued for 24 h. The organic solutionwasseparated, washed with water (50ml), dried (anhydrous magnesium sulphate), filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography eluting with DMAW 240 to give the title compound as a white solid (35mg, 12%). Mass spectrum 468 $[M+H]^+$.

Further examples according to reaction schemes 1-11 with coresponding mass data:

Systematic name	Structure	m/z $[M + H]^+$
1-Cyclopentylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		465
1-Cyclohexylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		493

1-Benzyl-3-(4-chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		597/599 (contains chlorine)
1,3-Dibenzyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea		577
1-Benzyl-1-{1-[2-(2-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea		449
4-(3-Benzyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-ureido)-benzoic acid		593
1-(4-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		563

1-(2,4-Dimethyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea		577

Example I

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient (preferabyly a compound as listed in table 1)	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example II

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient (preferabyly a compound as listed in table 1)	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

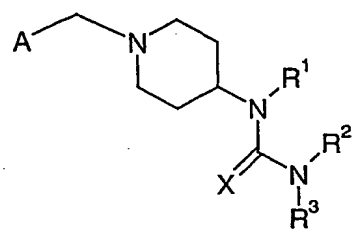
Example III

Capsules of the following composition are produced:

	mg/Capsule
Active ingredient (preferabyly a compound as listed in table 1)	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

Claims

1. Compounds of formula I



I

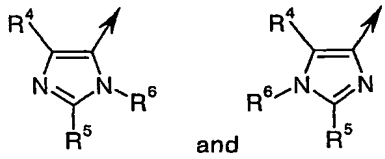
wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

X is S or O;

A is selected from the group consisting of:



A1 and A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, CN, COR, CO_2R, CONRR', NHCOR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR';

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, halogen, COR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR';

R^6 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{3-8}-cycloalkyl, COR, CO_2R, CONRR', NHCOR, SO_2NRR' or SO_2R;

R and R' are independently of each other hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

as well as ethers or hydrolyzable esters of compounds of formula I and pharmaceutically acceptable salts thereof.

2. Compound as claimed in claim 1 wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

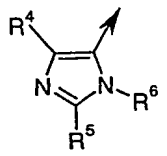
R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

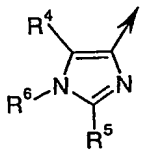
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, CN, COR, CO_2R, CONRR', NHCOR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl, substituted aryl-C(=O)- or substituted aryl-CH(OH)- are substituted with 1-5 substituents selected from

C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted heterocyclyl, substituted heterocyclyl-C(=O)- or substituted heterocyclyl-CH(OH)- are substituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, halogen, COR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl, substituted aryl-C(=O)- or substituted aryl-CH(OH)- are substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted heterocyclyl, substituted heterocyclyl-C(=O)- or substituted heterocyclyl-CH(OH)- are substituted with 1-4 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^6 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{3-8}-cycloalkyl, COR, CO_2R, CONRR', NHCOR, SO_2NRR' or SO_2R,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted

heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens;

R and R' are independently of each other hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl are substituted with 1-5 substituents and substituted heterocyclyl are substituted with 1-4 substituents, these substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR^7, CO_2R^7, $CONR^7R^8$, NR^7R^8, $NHCOR^7$, $SO_2NR^7R^8$, SO_2R^7, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^7 and R^8 are independently of each other hydrogen or C_{1-4}-alkyl.

3. Compounds as claimed in any one of claims 1 to 2 wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl or heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR',

SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

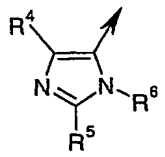
R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

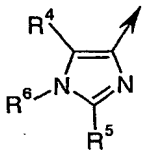
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, CO_2R or aryl;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, aryl, substituted aryl, aryl-C(=O)-, aryl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy,

halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted aryl means aryl substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, aryl, heterocyclyl, substituted aryl and substituted heterocyclyl; wherein substituted aryl and substituted heterocyclyl means aryl and heterocyclyl substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens;

R and R' are independently of each other hydrogen or C_{1-12}-alkyl.

4. Compounds as claimed in any one of claims 1 to 3 wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl, substituted phenyl and substituted pyridyl; wherein substituted phenyl and substituted pyridyl are substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

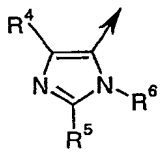
R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl, substituted phenyl and substituted pyridyl; wherein substituted phenyl or substituted pyridyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', SO_2R, NHCOR, SO_2NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

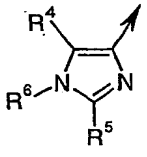
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, heterocyclyl, substituted phenyl and substituted heterocyclyl; wherein substituted phenyl and substituted heterocyclyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR',

NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, heterocyclyl, substituted phenyl and substituted heterocyclyl; wherein substituted phenyl or substituted heterocyclyl are substituted with C_{1-4}-alkoxy, halogen, CN, NO_2, COR, CO_2R, CONRR', NRR', NHCOR, SO_2NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens;

R and R' are independently of each other hydrogen or C_{1-12}-alkyl.

5. Compounds as claimed in any one of claims 1 to 4 wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, phenyl, phenoxy, halogen, CN, NO_2, CO_2R, NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

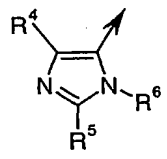
R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, halogen, NO_2, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, halogen, CN, NO_2, CO_2R, NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

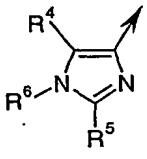
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl and substituted phenyl, wherein substituted phenyl is substituted with C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 halogens;

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl and substituted phenyl; wherein substituted phenyl is substituted with C_{1-4}-alkoxy, halogen, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 halogens;

R and R' are independently of each other hydrogen or C_{1-12}-alkyl.

6. Compounds as claimed in any one of claims 1 to 5 wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-8}-cycloalkyl, phenyl, pyridyl and substituted phenyl, wherein substituted phenyl is substituted with C_{1-4}-alkoxy, phenyl, phenoxy, chlorine, CN, NO_2, CO_2R, NRR', SO_2R, C_{1-4}-alkyl or C_{1-4}-alkyl substituted with 1-3 fluorines, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, chlorine, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 fluorines;

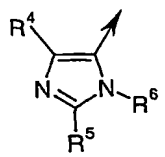
R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, substituted C_{1-4}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl, wherein substituted phenyl is substituted with NO_2, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-4}-alkoxy, fluorine, chlorine, CN, NO_2, CO_2R, NRR', C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 fluorines;

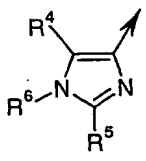
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-4}-alkoxy, chlorine, C_{1-4}-alkyl and C_{1-4}-alkyl substituted with 1-3 fluorines;

R^6 is hydrogen, C_{1-12}-alkyl or substituted C_{1-4}-alkyl,

wherein substituted C_{1-4}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl;

R and R' are independently of each other hydrogen or C_{1-12}-alkyl.

7. Compounds as claimed in any one of claims 1 to 6 wherein

R^1 is hydrogen, C_{1-7}-alkyl, C_{3-6}-cycloalkyl, allyl, substituted C_{1-2}-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-6}-cycloalkyl, phenyl, pyridyl and substituted phenyl,
wherein substituted phenyl is substituted with C_{1-2}-alkoxy, phenyl, phenoxy, chlorine, CN, NO_2, CO_2R, NRR', SO_2R, C_{1-2}-alkyl or C_{1-2}-alkyl substituted with 1-3 fluorines, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-2}-alkoxy, chlorine, C_{1-2}-alkyl and C_{1-2}-alkyl substituted with 1-3 fluorines;

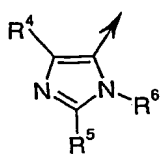
R^2 and R^3 are independently of each other hydrogen, C_{1-7}-alkyl, C_{3-6}-cycloalkyl, substituted C_{1-2}-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl, wherein substituted phenyl is substituted with NO_2, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_{1-2}-alkoxy, fluorine, chlorine, CN, NO_2, CO_2R, NRR', C_{1-2}-alkyl and C_{1-2}-alkyl substituted with 1-3 fluorines;

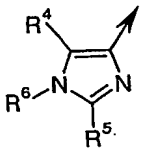
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-7}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-7}-alkyl, substituted C_{1-2}-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_{1-2}-alkoxy, chlorine, C_{1-2}-alkyl and C_{1-2}-alkyl substituted with 1-3 fluorines;

R^6 is hydrogen, C_{1-7}-alkyl or substituted C_{1-2}-alkyl,

wherein substituted C_{1-2}-alkyl means alkyl substituted with 1-3 substituents selected from phenyl;

R and R' are independently of each other hydrogen or C_{1-7}-alkyl.

8. Compounds as claimed in any one of claims 1 to 7 wherein

R^1 is hydrogen, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, allyl, substituted C_1-alkyl, phenyl, substituted phenyl or pyridyl,

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from C_{3-6}-cycloalkyl, phenyl, pyridyl and substituted phenyl, wherein substituted phenyl is substituted with C_1-alkoxy, phenyl, phenoxy, chlorine, CN, NO_2, CO_2R, NRR', SO_2R, C_1-alkyl or C_1-alkyl substituted with 1-3 fluorines, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_1-alkoxy, chlorine, C_1-alkyl and C_1-alkyl substituted with 1-3 fluorines;

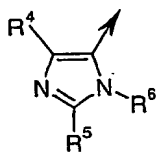
R^2 and R^3 are independently of each other hydrogen, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, substituted C_1-alkyl, phenyl, substituted phenyl, heterocyclyl or substituted heterocyclyl,

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, pyridyl and substituted phenyl, wherein substituted phenyl is substituted with NO_2, and

wherein substituted phenyl is substituted with 1-5 substituents and substituted heterocyclyl means heterocyclyl substituted with 1-4 substituents and these substituents are selected from C_1-alkoxy, fluorine, chlorine, CN, NO_2, CO_2R, NRR', C_1-alkyl and C_1-alkyl substituted with 1-3 fluorines;

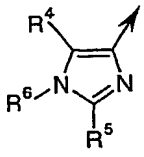
X is S or O;

A is selected from the group consisting of:



A1

and



A2

wherein

R^4 is hydrogen, C_{1-4}-alkyl, CO_2R or phenyl;

R^5 is hydrogen, C_{1-4}-alkyl, substituted C_1-alkyl, halogen, phenyl, substituted phenyl, phenyl-C(=O)-, phenyl-CH(OH)- or NRR',

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from phenyl, and

wherein substituted phenyl is substituted with 1-5 substituents selected from C_1-alkoxy, chlorine, C_1-alkyl and C_1-alkyl substituted with 1-3 fluorines;

R^6 is hydrogen, C_{1-5}-alkyl or substituted C_1-alkyl,

wherein substituted C_1-alkyl means alkyl substituted with 1-3 substituents selected from phenyl;

R and R' are independently of each other hydrogen or C_{1-4}-alkyl.

9. Compounds as claimed in any one of claims 1 to 8 wherein

X is O.

10. Compounds as claimed in any one of claims 1 to 9 wherein

A is A1.

11. Compounds as claimed in any one of claims 1 to 9 wherein

A is A2.

12. A compound as claimed in claim 1 which compound is

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea,

3-Methyl-1-[1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-phenylurea,

3-Methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-phenylurea,

1,1-Dimethyl-3-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-3-phenylurea,

1-Benzyl-3-methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea,

1-(4-Methoxyphenyl)-3-methyl-1-[1-[(5-methyl-2-phenyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea,

1-Benzyl-3-methyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

3-Methyl-1-[1-[[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylurea,

1-[1-[[2-(4-Chlorophenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea,

3-Methyl-1-phenyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-[1-[[2-(2,3-Dimethoxyphenyl)-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea,

1-[1-[[2-(2,3-Dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea,

1-Benzyl-3-methyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

3-Methyl-1-phenyl-1-[1-[[5-phenyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

3-Methyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-phenylthiourea,

1-Benzyl-3-methyl-1-[1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]urea,

1-Benzyl-1-[1-[(2-iodo-5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-3-methylurea,

1-Allyl-1-[1-[[5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-nitrobenzyl)urea,

1-[1-[(2-Benzoyl-5-methyl-1H-imidazol-4-yl)methyl]-4-piperidinyl]-1-benzyl-3-methylurea,

1-Benzyl-1-[1-[[2-[(RS)-(hydroxy)(phenyl)methyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea,

1-Benzyl-1-[1-[[1-benzyl-5-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea,

1-Benzyl-1-[1-[[3-benzyl-5-methyl-2-[4-(trifluoromethyl)phenyl]-3H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea,

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1,3-dimethylurea,

1-Butyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea,

1-Cyclohexyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea,

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-(2-phenethyl)urea,

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-(3-phenylpropyl)urea,

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-(4-methoxybenzyl)-3-methylurea,

1-(4-Chlorobenzyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methylurea,

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-[(4-pyridyl)methyl]urea,

1-Benzyl-3-ethyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-propylurea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-phenylurea,

1-Benzyl-1-[1-[[2-[4-trifluoromethyl-phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-methoxyphenyl)urea,

1-Benzyl-3-[4-(trifluoromethyl)phenyl]1-[1-[[2-[4-(trifluoromethyl)phenyl-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1,3-Dibenzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-3-cyclohexyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-3-tert.-butyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(2-phenylethyl)urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3-phenylpropyl)urea,

1-[1-[[2-[4-(Trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-1-(2,4,6-trimethoxybenzyl)-3-methylurea,

1-Allyl-1-[1-[[1-(2-chlorobenzoyl)-4(R)-phenyl-3(R)-pyrrolidinyl]methyl]-piperidin-4-yl]-3-(4-nitrobenzyl)urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(2-methylphenyl)urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3-methylphenyl)urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-methylphenyl)urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3,4-dimethylphenyl)urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(3,5-dimethylphenyl)urea,

1-Benzyl-3-(2-chlorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-3-(3-chlorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-3-(3,5-dichlorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-3-(4-fluorophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-[4-(dimethylamino)phenyl]urea,

1-Benzyl-3-(4-cyanophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-(4-nitrophenyl)urea,

1-Benzyl-3-(3-bromophenyl)-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-Benzyl-3-[3-(trifluoromethyl)phenyl]-1-[1-[[2-[4-(trifluoromethyl)phenyl]-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]urea,

1-[1-[[2-(2-Methoxyphenyl)-5-methyl-1H-imidazol-4-yl]methyl]-4-piperidinyl]-3-methyl-1-phenylurea,

Methyl 5-[[4-(1-benzyl-3-methylureido)piperidino]methyl]-2-[4-(trifluoromethyl)phenyl]-3H-imidazole-4-carboxylate,

1-Benzyl-1-[1-[5-methyl-2-(4-methylphenyl)-1H-imidazol-4-ylmethyl]-4-piperidinyl]-3-phenylurea,

1-Methyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Ethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-propyl-urea,

1-Isopropyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Allyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Isobutyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-tert.-butyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Cyclopropyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Cyclopropylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Cyclobutylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Cyclopentylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Cyclohexylmethyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-(2-Methoxy-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-(4-Methoxy-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-(2-Chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-(4-Chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(2-trifluoromethyl-phenyl)-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-trifluoromethyl-phenyl)-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-trifluoromethyl-benzyl)-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-4-yl-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-3-yl-urea,

3-Methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-pyridin-3-ylmethyl-urea,

1-Benzyl-3,3-diethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Benzyl-3-(4-chloro-phenyl)-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1,3-Dibenzyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Benzyl-3-cyclopropyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Benzyl-1-[1-(2-benzyl-5-methyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-3-methyl-urea,

1-Benzyl-3-methyl-1-[1-(5-methyl-2-phenylamino-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-urea,

1-Benzyl-1-{1-[2-(2-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea,

1-Benzyl-1-{1-[2-(4-tert.-butyl-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea,

1-Benzyl-3-(3,4-dichloro-phenyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

3-(4-Amino-phenyl)-1-benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

4-(3-Benzyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-ureido)-benzoic acid,

4-(3-Benzyl-3-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-ureido)-benzoic acid methyl ester,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-4-yl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-3-yl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-2-yl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridazin-3-yl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridazin-4-yl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-thiophen-2-yl-urea,

1-Benzyl-3-furan-2-yl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Benzyl-3-(5-methyl-[1,3,4]thiadiazol-2-yl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-4-ylmethyl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-3-ylmethyl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-pyridin-2-ylmethyl-urea,

1-Benzyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-(tetrahydro-pyran-4-yl)-urea,

1-Benzyl-3-(1-formyl-piperidin-4-yl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea,

1-(2,4-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(2-Chloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(2-Methoxy-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(2-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(3,5-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(3,4-Dichloro-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(3-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(4-Methyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(3-nitro-benzyl)-3-phenyl-urea,

1-(4-Dimethylamino-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-nitro-benzyl)-3-phenyl-urea,

1-(2,4-Dimethyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(4-Amino-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

4-(1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-ureidomethyl)-benzoic acid methyl ester,

1-(4-Methanesulfonyl-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-Biphenyl-3-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-Biphenyl-2-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-{1-[5-Methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-1-(4-phenoxy-benzyl)-3-phenyl-urea,

1-Biphenyl-4-ylmethyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

1-(4-Cyano-benzyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-phenyl-urea,

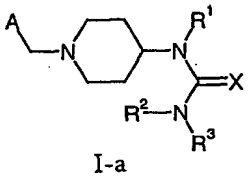
1-Benzyl-3-methyl-1-[1-(5-methyl-2-p-tolyl-1H-imidazol-4-ylmethyl)-piperidin-4-yl]-urea,

1-Benzyl-1-{1-[2-(4-methoxy-phenyl)-5-methyl-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-3-methyl-urea,

1-Cyclopentyl-3-methyl-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea, or

1-Benzyl-3-(4-iodo-phenyl)-1-{1-[5-methyl-2-(4-trifluoromethyl-phenyl)-1H-imidazol-4-ylmethyl]-piperidin-4-yl}-urea.

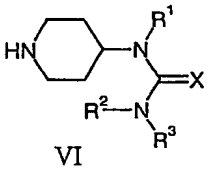
13. A process for the preparation of compounds of formula I-a



I-a

which process comprises

reacting a compound of formula VI



VI

a) with a carboxaldehyde of formula A-CHO,

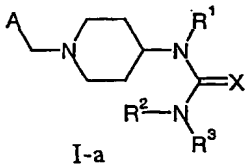
wherein A are as defined in formula I

and subsequently reducing the reaction product with a reducing agent; or

b) with a methylene halide of formula A-CH_2Hal,

wherein R^1, R^2, R^3, A and X are as defined in formula I and Hal is Cl, Br or I.

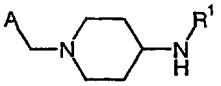
14. A process for the preparation of compounds of formula I-a



I-a

which process comprises

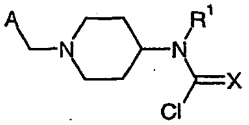
reacting a compound of formula X



X

a) with phosgene or thiophosgene of formula $X=CCl_2$,

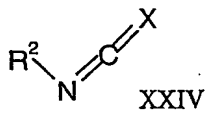
to obtain compound of formula XI



XI

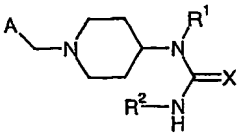
and subsequently reacting compound of formula XI with HNR^2R^3; or

b) with a compound of formula XXIV,



XXIV

and further reacting the compound of formula I-b



I-b

obtained with R^3-Hal,

wherein R^1, R^2, R^3, A and X are as defined for compounds of formula I and Hal is chlorine or bromine.

15. A compound as defined in any one of claims 1 to 12 for its use in the treatment of the human or animal body.

16. Use of the compounds as defined in any one of claims 1 to 12 for the preparation of a medicament for the treatment of diseases mediated by the human immunodeficiency virus (HIV).

17. A compound as claimed in any one of claims 1 to 12 for its use in the treatment of a disease mediated by the human immunodeficiency virus (HIV).

18. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound or a pharmaceutically acceptable salt thereof or defined in any one of claims 1 to 12 and, if desired, a pharmaceutical inert carrier.

19. A pharmaceutical composition according to claim 18 for its use in the treatment of diseases mediated by the human immunodeficiency virus (HIV).

20. The invention as hereinbefore described.

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Human Immunodeficiency Virus Type 1 Membrane Fusion Mediated by a Laboratory-Adapted Strain and a Primary Isolate Analyzed by Resonance Energy Transfer

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Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this study was to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory-adapted strain. To this end, a new fusion assay was developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1_{LAI} or the macrophage-tropic primary isolate HIV-1_{JR-FL}. These cells fused with CD4$^+$ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, HeLa cells expressing HIV-1_{JR-FL} gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1_{JR-FL} and HIV-1_{LAI} in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. Inhibition of HIV-1_{JR-FL} envelope glycoprotein-mediated membrane fusion by soluble CD4 and CD4-IgG2 occurred at concentrations similar to those required to neutralize this virus. Interestingly, higher concentrations of these agents were required to inhibit HIV-1_{LAI} envelope glycoprotein-mediated membrane fusion, in contrast to the greater sensitivity of HIV-1_{LAI} virions to neutralization by soluble CD4 and CD4-IgG2. This finding suggests that the mechanisms of fusion inhibition and neutralization of HIV-1 are distinct.

Following the binding of human immunodeficiency virus type 1 (HIV-1) gp120/gp41 to the cell surface receptor human CD4, a domain of gp41 mediates fusion of the viral and target cell membranes, resulting in the introduction of the viral capsid into the target cell cytoplasm (15). Cells expressing HIV-1 gp120/gp41 also fuse with CD4-expressing cells, leading to the formation of multinucleated giant cells, or syncytia. The initial events in syncytium formation are analogous to the attachment and fusion stages of viral entry (9). First, the cell membranes connect at localized sites; this connection is a rapid and reversible event. Later, the cells fuse irreversibly to form syncytia.

To date, real-time studies of HIV-1 envelope glycoprotein-mediated membrane fusion have been performed with strains of HIV-1 that have been extensively propagated in transformed human T-cell lines. While reporter gene assays have been used successfully to analyze the tropism of primary HIV-1 isolates (3), these have limited utility for analysis of the mechanisms and properties of the membrane fusion process. In order to analyze and compare membrane fusion mediated by the envelope glycoproteins of primary HIV-1 isolates and laboratory-adapted strains, we have developed a new resonance energy transfer (RET)-based fusion assay. This assay is modeled on methods designed to study membrane fusion mediated by mutants of herpes simplex virus type 1 (HSV-1) or cell fusion induced by polyethylene glycol (14, 32).

The RET assay measures HIV-1 envelope glycoprotein-mediated membrane fusion. This fluorescence-based technique involves labeling one fusion partner (an HIV-1 gp120/gp41-expressing cell line) with fluorescein octadecyl ester (F18; Molecular Probes, Eugene, Oreg.) and the other fusion partner (a CD4-expressing cell line) with octadecyl rhodamine (R18; Molecular Probes). These probes consist of fluorescent molecules conjugated to saturated hydrocarbon chains, 18 carbons long, which spontaneously insert into cell plasma membranes (14). They do not inhibit cellular replication or fusion efficiency (32). The fluorochromes are chosen such that the emission spectrum of one (F18) overlaps the excitation spectrum of the second (R18). Fusion results in the close association of the dyes in the plasma membrane, and thus transfer of the energy generated by F18 excitation to R18 is followed by emission at the R18 spectrum.

Briefly, F18 (5 mg/ml in ethanol) was diluted 1:1,000 in complete tissue culture medium containing 10% fetal bovine serum and adjusted such that the A_{506} was 0.34. R18 (10 mg/ml in EtOH) was similarly diluted such that the A_{565} was 0.52. Cells were incubated overnight in the fluorescent dye-containing culture medium. Fluorochrome-labeled adherent cells were removed from culture flasks by treatment with 0.5 mM EDTA and washed several times in culture medium containing 10% fetal bovine serum. HeLa-env cells (2×10^4) were plated with an equal number of CD4-expressing cells per well in a 96

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TABLE 1. HIV-1 envelope glycoprotein-mediated membrane fusion determined by RET

R18-labeled cells	% RET for fusion with F18-labeled cells[a]				
	HeLa-env$_{LAI}$		HeLa-env$_{JR-FL}$		HeLa
	Alone	With OKT4A[b]	Alone	With OKT4A	
HeLa-CD4	10.7 ± 4.4	0.8 ± 0.7	1.0	ND[c]	0.5 ± 0.4
C8166	14.2 ± 1.6	1.3 ± 1.1	2.3 ± 0.4	ND	1.3 ± 0.9
Sup-T1	18.7 ± 1.0	0	0	ND	0
HUT 78	8.2 ± 1.6	0.9 ± 0.6	1.0 ± 1.6	ND	1.0 ± 1.6
PM1	5.0 ± 3.9	1.0 ± 0.6	10.2 ± 3.7	1.1 ± 0.6	0.6 ± 0.7
CHO-CD4[d]	0.3	ND	0.3	ND	0.2
U87MG-CD4	0.7 ± 0.4	ND	0.6 ± 0.6	ND	1.2 ± 1.1

[a] The data are the means ± standard deviations for at least three independent assays, unless otherwise stated.
[b] At the initiation of culture, 0.3 μg of MAb per ml was added.
[c] ND, not determined.
[d] The results are the means for two assays.

well plate in a final volume of 200 μl and incubated for 4 h at 37°C. Controls included wells containing each cell line alone. Following three washes in phosphate-buffered saline (PBS), fluorescence was measured with a Cytofluor plate reader (PerSeptive Biosystems, Framingham, Minn.).

The emission values, X, Y, and Z, were recorded for the following cell combinations. A, HeLa-env cells and CD4-expressing cells; B, HeLa-env cells alone; and C, CD4-expressing cells alone. The following filter combinations were used. X, excitation at 450 nm and emission at 530 nm; Y, excitation at 530 nm and emission at 590 nm; and Z, excitation at 450 nm and emission at 590 nm. For example, A_Z is the measurement obtained by using cell combination A and filter combination Z. The output from the fluorescence plate reader was used to calculate percent RET.

The excitation and emission spectra of F18 and R18 are broad; therefore, when each dye is excited at 450 nm, there is a background emission of energy at 590 nm (B_z and C_z). Since this background, or spillover, fluorescence occurs in the absence of RET, the following calculation is used to correct for the spillover. F_{spill} and R_{spill} represent the F18 (B_Z/B_X and R18 (C_Z/C_Y) spillover coefficients which we have empirically determined to be 0.52 and 0.03, respectively.

$$\%\text{RET} = 100 \times \frac{A_Z - (A_X \times F_{spill}) - (A_Y \times R_{spill})}{A_Y}$$

The data are expressed as the percent RET, which is derived from a comparison of the RET value to the maximum R18 emission obtained by direct excitation of R18 at 530 nm (A_Y). Only a fraction of the maximum R18 emission is expected to be achieved via RET. This assumption was confirmed by double-labeling cells with both F18 and R18 and calculating the resultant percent RET. When HeLa, PM1 (obtained from R. Gallo and P. Lusso, National Institutes of Health [NIH], Bethesda, Md.) (19), or C8166 (obtained from R. Weiss, Institute of Cancer Research, London, England) cells, were double-labeled, RET values ranging from 15 to 20% were achieved. Accordingly, the largest theoretical RET value expected following fusion of cells would be in the range of 15 to 20%. Indeed, RET values in this range were often observed, indicating that highly efficient mixing of the plasma membranes and dyes occurred in the membrane fusion experiments.

When F18-labeled HeLa-env$_{LAI}$ cells (11) were incubated with R18-labeled HeLa-CD4 cells (20) for 4 h, RET values of approximately 11% were obtained (Table 1). In contrast, minimal RET levels (0.5%) were observed when F18-labeled HeLa cells were used instead of HeLa-env$_{LAI}$ cells (Table 1). When different ratios of F18-HeLa-env$_{LAI}$ and F18-HeLa cells were incubated with R18-HeLa-CD4 cells and the total number of F18-labeled cells was held constant, the level of RET was directly proportional to the number of input R18-HeLa-env$_{LAI}$ cells (data not shown), indicating that RET is proportional to the number of fusogenic cells present. Moreover, RET was detectable above background when only 10% of the input F18-labeled cells were fusogenic.

The monoclonal antibody (MAb) OKT4A, which inhibits the binding of HIV-1 gp120 to CD4 (21), abrogated RET in cocultures of HeLa-env$_{LAI}$ and CD4$^+$ cells (Table 1). No inhibition was observed with the control MAb OKT4 (data not shown). Several T-lymphoblastoid cells which are known to be susceptible to T-cell tropic strains of HIV-1 also specifically fused with the HeLa-env$_{LAI}$ cells (Table 1). HIV-1 is known to bind to, but not infect, rodent cells expressing human CD4; likewise, cells expressing HIV-1 gp120/gp41 will not fuse with rodent cells expressing human CD4 (20). When the R18-labeled CD4$^+$ Chinese hamster ovary transfectant (CHO-CD4; Progenics) was incubated with F18-labeled HeLa-env$_{LAI}$ cells, no RET was detected. Similarly, HeLa-env$_{LAI}$ cells did not fuse with the glioblastoma CD4 transfectant U87.MG-CD4 (obtained from P. Clapham, Institute of Cancer Research), which is one of the few CD4$^+$ human cell lines refractory to infection or fusion by HIV-1 (5, 6) (Table 1). Thus, conditions which allow cell-to-cell binding in the absence of membrane fusion did not result in RET. Taken together, these results demonstrate that with the RET assay, real membrane fusion events are determined and not the spontaneous transfer of fluorescent dyes between membranes in close proximity.

RET assay as a model system to investigate HIV-host cell tropism. In contrast to T-cell-tropic laboratory-adapted strains, macrophage-tropic primary isolates of HIV-1 do not infect CD4$^+$ T-cell lines and often exhibit reduced or no syncytium formation. In order to investigate membrane fusion mediated by a macrophage-tropic primary isolate of HIV-1, HeLa cells stably expressing the envelope glycoprotein from the macrophage-tropic primary isolate HIV-1$_{JR-FL}$ were generated (designated HeLa-env$_{JR-FL}$). The HIV-1$_{LAI}$ *env* gene was excised from the plasmid pMA243 (11) and the HIV-1$_{JR-FL}$ *env* gene was inserted by the splicing by overlap extension technique. The HIV-1$_{JR-FL}$ *env* gene was amplified from the plasmid pUCFL112-1 (provided by I. S. Y. Chen, University of California at Los Angeles) (17). The resultant plasmid, designated JR-FL-pMA243, was sequenced by the dideoxy method and introduced into HeLa cells by the lipofectin (Gibco BRL) method. HeLa-env$_{JR-FL}$ transfectants were selected in methotrexate (Sigma) and cloned twice by limiting dilution. Flow cytometric analysis with a MAb to the CD4 binding site on gp120, F105 (NIH AIDS Research and Reference Reagent Program) (26), indicated that HeLa-env$_{JR-FL}$ and HeLa-env$_{LAI}$ cells expressed comparable levels of HIV-1 envelope glycoprotein at the cell surface (Fig. 1). Next, the two cell lines were surface labeled with biotin, solubilized, and immunoprecipitated with F105 (26), a polyclonal sheep antibody (6205) to the carboxy terminus of gp120 (International Enzymes, Fallbrook, Calif.) (27), or CD4-IgG2 (Progenics) (1) by published procedures (13, 18, 22). The amount of gp120 in the precipitates was determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis followed by Western blotting (immunoblotting) and incubation with streptavidin-horseradish peroxidase and then detected by the enhanced chemiluminescence system (Amersham Life Sciences, Arlington Heights,

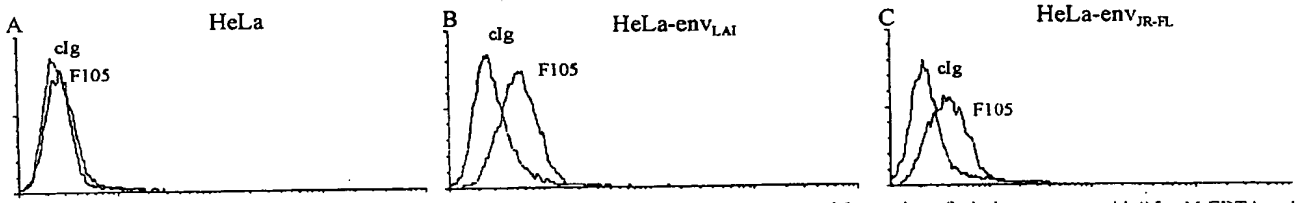

FIG. 1. Surface expression of HIV-1 envelope glycoprotein in HeLa transfectants. Cells were removed from culture flasks by treatment with 0.5 mM EDTA and washed in culture medium. HeLa (A), HeLa-env$_{LAI}$ (B), and HeLa-env$_{JR-FL}$ cells (C) were stained with 2 μg of F105 or 2 μg of isotype control antibody (clg) (Sigma) for 15 min at 4°C and washed three times in PBS containing 0.05% NaN_3. Next, cells were incubated in phycoerythrin-conjugated goat anti-human immunoglobulin (Southern Biotechnology Associates, Birmingham, Ala.), washed, and fixed in 0.2% paraformaldehyde. Samples were analyzed on a FACScan flow cytometer (Becton Dickinson, San Jose, Calif.). Fluorescence intensity is shown on the *x* axis (four decade log scale), and the relative number of cells is indicated on the *y* axis.

Ill.) (data not shown). These analyses indicated that the levels of gp120 expression on the surfaces of the two cell lines are similar, with differences in the levels detected of no more than twofold.

Background levels of RET, indicating the absence of membrane fusion, were obtained when HeLa-env$_{JR-FL}$ cells were mixed with HeLa-CD4 cells and most CD4$^+$ T-cell lines (C8166, HUT 78 and Sup-T1) (NIH AIDS Research and Reference Reagent Program) (Table 1). Similar results were obtained when HeLa-env$_{JR-FL}$ cells were mixed with the T:B hybrid CEM × 174 (28, 30) (NIH AIDS Research and Reference Reagent Program) or the macrophage cell lines U937 or phorbol myristate acetate-treated THP-1 (American Type Culture Collection) (30) (data not shown). The recently described CD4$^+$ T-cell line PM1 is the only cell line permissive to infection by both macrophage-tropic and T-cell-tropic HIV-1 isolates, including HIV-1$_{JR-FL}$ (2, 19). PM1 was derived as a direct clone of the HUT 78 T-cell line, selected on the basis of infectibility by the macrophage-tropic isolate HIV-1$_{BaL}$ (19). PM1 cells fused substantially with HeLa-env$_{JR-FL}$ cells (10% RET) (Table 1) but not with HeLa cells (0.6% RET) (Table 1). Membrane fusion between PM1 and HeLa-env$_{JR-FL}$ was completely inhibited in the presence of OKT4A (Table 1). Similar to that with HeLa-env$_{LAI}$, no membrane fusion was observed between HeLa-env$_{JR-FL}$ and CHO-CD4 or U87MG-CD4 (Table 1).

In RET analysis, the tropism of membrane fusion mediated by the HIV-1$_{LAI}$ and HIV-1$_{JR-FL}$ envelope glycoproteins mirrored that of the respective viruses. This observation is consistent with the concept that the envelope glycoprotein is a major determinant of HIV-1 tropism (3, 16, 24, 29). Furthermore, the results obtained with combinations of HeLa-env$_{JR-FL}$ and PM1 cells demonstrate that membrane fusion mediated by gp120/gp41 from a macrophage-tropic primary HIV-1 isolate occurs at neutral pH.

Characterization of HIV-1 envelope glycoprotein-mediated membrane fusion by RET. Calcium ions are known to be required for the fusion of biological membranes. Dimitrov et al. established that HIV-1$_{IIIB}$ envelope glycoprotein-mediated membrane fusion and syncytium formation require the presence of calcium ions, whereas the binding of gp120 to CD4 is calcium independent (8). The RET generated by fusion between HeLa-env$_{LAI}$ or HeLa-env$_{JR-FL}$ and CD4$^+$ target cells decreased by more than 50% in the presence of concentrations greater than 2.25 mM EDTA, a chelator of divalent cations (data not shown). These experiments demonstrate that, as with laboratory-adapted strains, membrane fusion mediated by the envelope glycoprotein of a macrophage-tropic primary isolate of HIV-1 is dependent on the presence of divalent cations.

The kinetics of membrane fusion were examined by the RET assay. Specific membrane fusion was first detected by the RET assay at 90 min and increased up to 4 h, with similar results being obtained with HeLa-env$_{LAI}$ and HeLa-env$_{JR-FL}$ (Fig. 2). Beyond 4 h, there was no further increase in the percentage of specific RET (data not shown). These results are consistent with previous reports of fusion mediated by a laboratory-adapted strain of HIV-1 (9) and demonstrate that the rates of fusion mediated by gp120/gp41 from a laboratory-adapted strain and a primary isolate of HIV-1 are similar.

Syncytium formation. The tropism of HIV-1$_{LAI}$ and HIV-1$_{JR-FL}$ envelope glycoproteins in the RET assay was mirrored by the development of syncytia in cocultures of HeLa-env cells with CD4$^+$ target cell lines (data not shown). For example, syncytia were observed in cocultures of HeLa-env$_{JR-FL}$ with PM1 cells but not with C8166 or HeLa-CD4 cells. While syncytium formation between HeLa-env$_{LAI}$ cells and HeLa-CD4 or C8166 was apparent at 4 h, there was a substantial increase in both the number and size of multinucleated cells by 24 h. In contrast, membrane fusion was maximal after 4 h in the RET assay (Fig. 2). This delay between membrane fusion and visible syncytia has previously been observed with cells expressing gp120/gp41 from the laboratory-adapted strain HIV-1$_{IIIB}$ (9, 12). In the present study, a similar delay was found between membrane fusion and visible syncytium formation in cocultures of HeLa-env$_{JR-FL}$ and PM1 cells. While membrane fusion was maximal at 4 h (Fig. 2), few syncytia were noted at this time point, although many were evident at 24 h (data not shown).

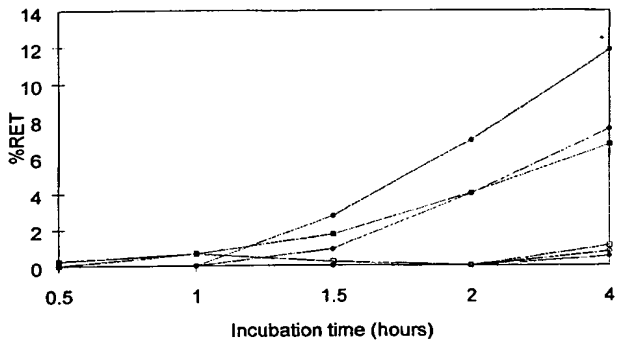

FIG. 2. Time course of HIV-1$_{LAI}$ and HIV-1$_{JR-FL}$ envelope glycoprotein-mediated membrane fusion by the RET assay. The rate of membrane fusion between HeLa-env$_{LAI}$ and HeLa-CD4 (■) or C8166 (●) and HeLa-env$_{JR-FL}$ and PM1 (◆) was determined by the RET assay. Cells were mixed, and the percent RET was determined at various intervals thereafter. Nonspecific RET, defined as the percent RET generated when HeLa cells were mixed with HeLa-CD4 (□), C8166 (○), or PM1 (◇) cells, was also evaluated at each time point.

TABLE 2. Inhibition of RET by CD4-based proteins[a]

F18-labeled cells	R18-labeled cells	IC_{50} (μg/ml)	
		sCD4	CD4-IgG2
HeLa-env_{JR-FL}	PM1	30.5	1.2
HeLa-env_{LAI}	PM1	38.9	7.2
	C8166	54.5	17.0
	HeLa-CD4	88.3	26.6

[a] Inhibitors were added simultaneously with the cells at the initiation of the 4-h incubation. Six twofold dilutions of sCD4 and CD4-IgG2 were added at concentrations ranging from 200 to 6.25 μg/ml and 42 to 1.2 μg/ml, respectively. The difference in potency of sCD4 and CD4-IgG2 is fourfold greater on the basis of molarity than on the basis of mass, since the molecular masses of the proteins are 46 and 200 kDa, respectively. Data are the means for at least three independent experiments which were run in duplicate.

Inhibition of membrane fusion determined by RET assay. Antibodies to CD4 and the HIV-1 envelope glycoprotein inhibit membrane fusion. For example, OKT4A exhibited similar levels of inhibition of RET mediated by the primary isolate, HIV-1_{JR-FL} (50% inhibitory concentration [IC_{50}], 15.7 ng/ml), and the laboratory-adapted strain HIV-1_{LAI} (IC_{50}, 11.7 ng/ml). The human MAb 2F5, which recognizes a conserved region of gp41 (4), inhibited membrane fusion mediated both by HIV-1_{LAI} and HIV-1_{JR-FL} with an IC_{50} of approximately 50 μg/ml.

CD4-IgG2 is a CD4-Ig fusion protein in which the variable regions of both the heavy and light chains of human IgG2 have been replaced by the N-terminal domains of CD4 (1). This heterotetramer potently neutralizes laboratory-adapted strains and primary isolates of HIV-1 (1, 31). CD4-IgG2 substantially inhibited HIV-1 envelope glycoprotein-mediated membrane fusion detected by RET (Table 2). A comparison of the IC_{50} values demonstrates that membrane fusion between HeLa-env_{JR-FL} and PM1 cells was more sensitive to inhibition by CD4-IgG2 than was fusion between HeLa-env_{LAI} and PM1, HeLa-CD4, or C8166. Although a less potent inhibitor than CD4-IgG2, soluble CD4 (sCD4) (Progenics) also inhibited HIV-1 envelope glycoprotein-mediated membrane fusion (Table 2). However, the HeLa-env_{JR-FL} and HeLa-env_{LAI} assays exhibited smaller differences in sensitivity to inhibition by sCD4 than by CD4-IgG2.

In contrast to these results, the results of previous studies have shown that HIV-1_{LAI} is approximately 1,500-fold more sensitive than HIV-1_{JR-FL} to neutralization by sCD4 and 15-fold more sensitive to CD4-IgG2 (1, 7). It has been demonstrated that differences between the sensitivities of primary and laboratory-adapted HIV-1 strains to neutralization by CD4-based molecules may result from either differences in affinity of CD4 for the membrane-associated oligomeric envelope glycoprotein or differences in dissociation of gp120 from gp41 by CD4-based molecules (23, 25). Analysis by flow cytometry indicates that CD4-IgG2 bound more readily to HeLa-env_{JR-FL} cells than to HeLa-env_{LAI} cells (Fig. 3). This was true over a wide range of concentrations (0.063 to 32 μg/ml), even though these cells express similar levels of surface gp120 (Fig. 1). Previous reports have demonstrated that under the incubation conditions used for flow cytometry in the present study (15 min at 4°C), CD4-based molecules induce minimal shedding of gp120 from laboratory-adapted strains of HIV-1 (23). Therefore, these results suggest that CD4-IgG2 binds more avidly to the oligomeric envelope glycoprotein of HIV-1_{JR-FL} than to that of HIV-1_{LAI}.

Dimitrov et al. reported a similar discrepancy in the potency of sCD4 in neutralization and cell fusion assays for the laboratory-adapted strain HIV-1_{IIIB} (10) and suggested that dissociation of gp120 from HIV-1_{IIIB} virions may have a more important role in virus neutralization than in the inhibition of cell membrane fusion (10). Other studies have found that CD4-based proteins are much less effective at dissociating gp120 from primary isolates of HIV-1 than from laboratory-adapted strains at 37°C (23, 25). This may explain why, in contrast to laboratory-adapted HIV-1 strains, the IC_{50} values for inhibition of HIV-1_{JR-FL} envelope glycoprotein-mediated membrane fusion by CD4-based proteins determined by the RET assay (e.g., with CD4-IgG2, IC_{50} of 1.2 μg/ml) are similar to those previously reported in neutralization studies with this isolate (with CD4-IgG2, IC_{50} of 3.5 μg/ml) (1).

The RET assay permits real-time determinations of membrane fusion mediated by gp120/gp41 from a primary isolate and a laboratory-adapted strain of HIV-1. We have shown that the fusogenicity of cells expressing the envelope glycoproteins of these viruses mimics the tropism of the viruses, indicating that gp120/gp41 is a major determinant of tropism. Presumably, PM1 cells are permissible for fusion with HeLa-env_{JR-FL} cells because the PM1 clone expresses one or more fusion accessory molecules not present in the parental HUT 78 line. However, a phenotypic analysis of these cell lines did not indicate any difference in expression of a panel of 15 leukocyte surface markers. Like HUT 78, PM1 cells display some T-cell markers ($CD3^+$, $CD4^+$, and $CD26^+$) but not others ($CD2^-$ and $CD7^-$), and both cells display some macrophage markers ($CD11c^+$ and $CD33^+$) (data not shown). The RET assay provides a valuable system for the further analysis of the determinants of HIV-1 tropism, which is currently underway.

Despite significant differences exhibited by HIV-1_{JR-FL} and HIV-1_{LAI} in terms of tropism and sensitivity to neutralization by CD4-based proteins, in the present study membrane fusion mediated by the envelope glycoproteins of these viruses showed remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar for the laboratory-adapted strain and the primary isolate. Membrane fusion mediated by both isolates occurred at neutral pH and was dependent on the presence of divalent cations. Moreover,

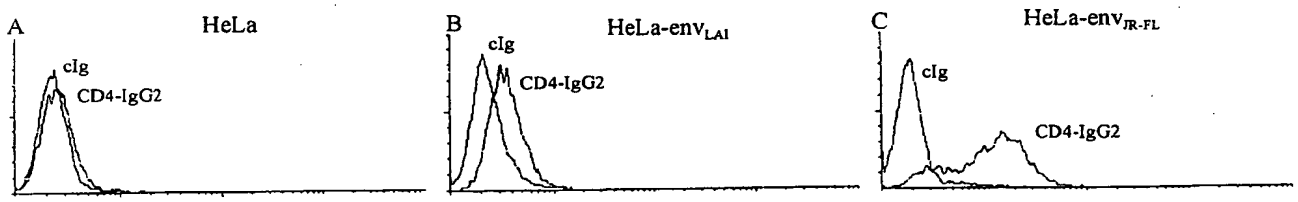

FIG. 3. CD4-IgG2 binding to HeLa-env transfectants. HeLa (A), HeLa-env_{LAI} (B), and HeLa-env_{JR-FL} (C) cells were incubated with 20 ng of CD4-IgG2 or 20 ng of human IgG2 (cIg) followed by phycoerythrin-conjugated goat anti-human immunoglobulin. Samples were analyzed on a FACScan flow cytometer. Fluorescence intensity is shown on the *x* axis (four decade log scale), and the relative number of cells is indicated on the *y* axis. The data are representative of at least three assays.

both isolates exhibited similar levels of sensitivity to inhibition by MAbs directed against CD4 and gp41.

Finally, it was demonstrated that the relative levels of sensitivity of membrane fusion mediated by the two HIV-1 strains to inhibition by CD4-based proteins did not reflect the greater sensitivity of HIV-1_{LAI} than of HIV-$1_{JR\text{-}FL}$ to neutralization by these agents, indicating that the mechanisms of membrane fusion inhibition and neutralization of HIV-1 are distinct.

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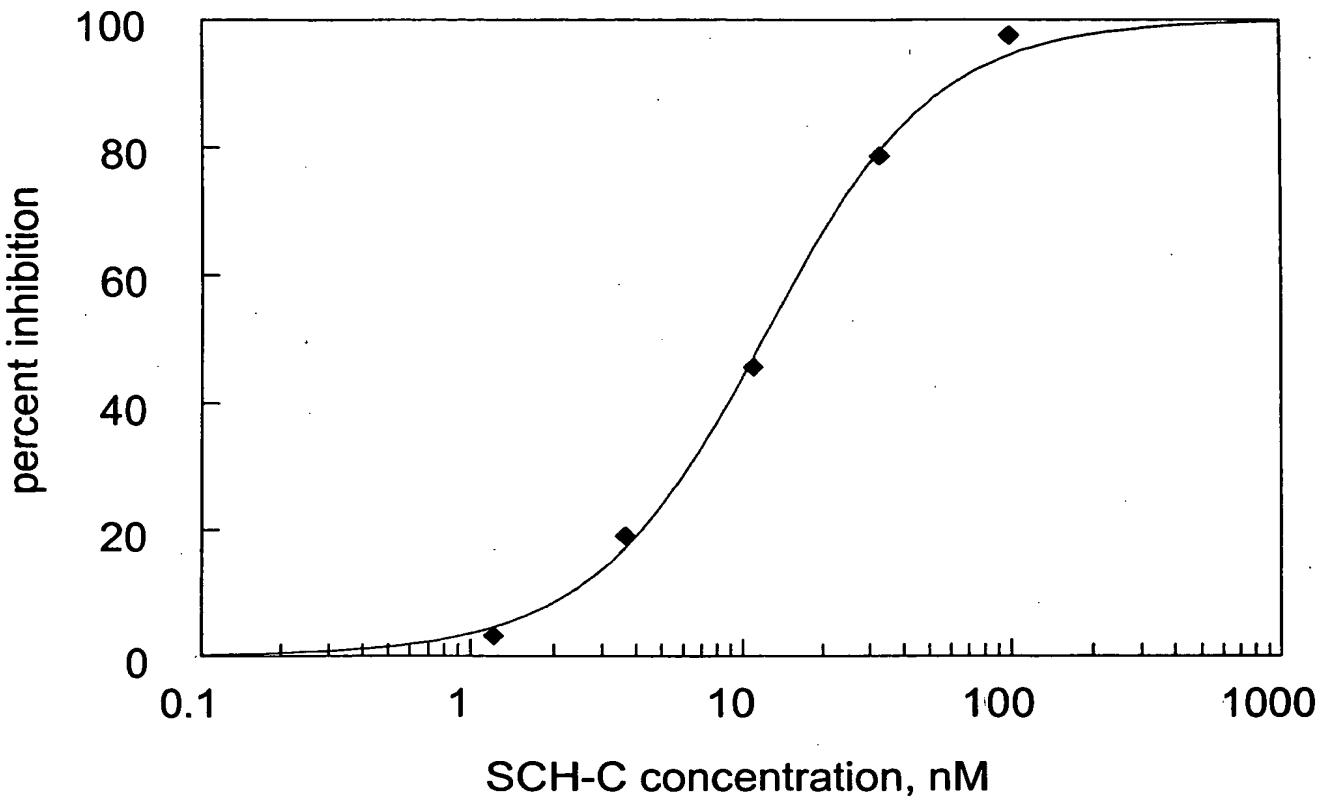

Methods. SCH-C (SCH 351125) was tested for inhibition of HIV-1_{JR-FL} envelope-mediated membrane fusion in a fluorometric resonance energy transfer assay (Litwin et al., 70:6437, 1996). The data are representative of three independent assays. Briefly, SCH-C was synthesized as previously described (Palani et al., J. Med.Chem. 45:3143, 2002). HeLa cells that stably express the envelope glycoproteins of the primary R5 virus HIV-1_{JR-FL} were membrane-labeled overnight with octadecyl fluorescein (F18; Molecular Probes, Eugene, OR), while PM1 cells were similarly labeled with octadecyl rhodamine (R18). PM1 is a T cell line that endogenously expresses CCR5 as well as CXCR4 and supports entry of R5 and X4 viruses. After labeling, the cells were washed in PBS containing 15% fetal bovine serum (PFBS buffer) and combined in equal numbers in 96-well microtiter plates (Becton-Dickinson, Franklin Lakes, NJ) in PFBS buffer. Serially diluted inhibitors were added at this time either individually or in combination in a fixed concentration ratio. The plates were incubated for 4h at 37 °C and then read on a fluorescence plate reader (PE Biosystems, Foster City, CA). Fluorescent RET from F18 to R18 occurs only when the dyes are placed in the same cellular membrane following fusion, and thus can be directly related to the extent of HIV-1 membrane fusion. RET observed in the presence of inhibitor was compared with that observed in their absence (0% inhibition) and in the presence of the anti-CD4 antibody Leu 3a (100% inhibition; Becton-Dickinson). The HeLa envelope cell lines can be prepared using the methods described in the original publication (Litwin et al., 70:6437, 1996). PM1 cells are available from the NIH AIDS Research and Reference Reagent Program (Cat. # 3038). The IC50 (concentration of SCH-C required to inhibit HIV-1 fusion by 50%) was 12 nM.

Antiretroviral Chemotherapy: New Agents

Monday, 10 am - 12:30 pm, 6A-B

1 SCH C: Safety and Antiviral Effects of a CCR5 Receptor Antagonist in HIV-1-Infected Subjects

J. Reynes[1], R. Rouzier[2], T. Kanouni[2], V. Baillat[2], B. Baroudy[3], A. Keung[3], C. Hogan[4], M. Markowitz[4], and M. Laughlin*[3]

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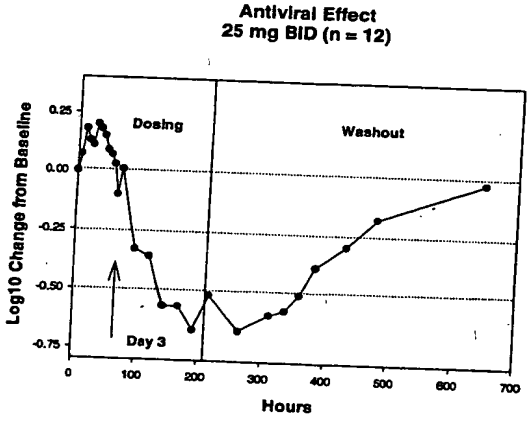
Background: SCH C is an orally bioavailable CCR5 receptor antagonist with potent *in vitro* antiviral activity against a broad selection of primary HIV-1 isolates. The safety and tolerability as well as pharmacokinetic profile have been described in healthy volunteers to doses as high as 600 mg as a single dose (mean Cmax ~2100 nM) and 400 mg/day as multiple (14 days) doses (mean Cmax ~1400 nM). Prolongation of the QTc interval was noted at the 600-mg single dose and at the 400-mg/day multiple dose level. The *in vivo* potential for antiviral effects of SCH C is currently being investigated in an ongoing, sequential rising dose trial (12 subjects/group) as monotherapy with daily doses of 50 mg, 100 mg, and 200 mg in HIV-infected subjects

Methods: 12 adults chronically infected with HIV J currently on no antiretroviral agents and with CD4+ cell counts above 250/mm^3 were administered 25 mg SCH C orally every 12 hours for 10 days. HIV-1 RNA levels were determined every 6 hours for 72 hours and then every 24 hours for the remaining 10 days of dosing. In addition, periodic HIV-1 RNA levels were determined during 18 days of follow-up. Subjects had SI/NSI phenotyping prior to dosing, at the end of dosing and at follow-up. Subjects with an SI phenotype at baseline were excluded from participation. The pharmacokinetic profile was determined.

Results: SCH C was safe and well tolerated. Preliminary analysis of the pharmacokinetic profile was similar to healthy volunteers with mean Cmax and Cmin levels at steady state of approximately 140 M and 90 nM, respectively. The figure shows the antiviral effects of SCH C over the 10 days of dosing and during washout. As shown there is a short lag time in effect as well as a prolonged effect following cessation of dosing. 10 of 12 subjects had at least a 0.5 $\log_{10}$ reduction from baseline during dosing, with 4 subjects achieving 1.0 $\log_{10}$ or greater reduction.



Conclusion: Preliminary data with SCH C supports the CCR5 receptor as a viable target for antiretroviral therapy.

2 AMD-3100, a CXCR4 Antagonist, Reduced HIV Viral Load and X4 Virus Levels in Humans

D. Schols*[1], S. Claes[1], E. De Clercq[1], C. Hendrix[2], G. Bridger[3], G. Calandra[3], G. W. Henson[3], S. Fransen[4], W. Huang[4], J. M. Whitcomb[4], C. J. Petropoulos[4], and AMD-3100 HIV Study Group

[1]*Rega Inst., Leuven, Belgium;* [2]*Johns Hopkins Sch. of Med., Baltimore, MD;* [3]*AnorMED Inc., Langley, BC, Canada; and* [4]*ViroLogic Inc., San Francisco, CA*

Background: The antiviral efficacy of the CXCR4 antagonist AMD-3100 was evaluated in an open-label, non-comparative, dose-escalating phase IIa trial in HIV-positive patients, where AMD-3100 was given in a 10-day continuous infusion. A retrospective longitudinal analysis was performed on patient plasma samples using a new PhenoSense HIV entry assay that measures co-receptor tropism and susceptibility to entry inhibitors.

Methods: 40 patients with plasma HIV RNA >5000 copies/mL on stable ART/no ART received doses of AMD-3100 ranging from 2.5 mcg/kg/h to 160 mcg/kg/h and were evaluated for safety, PK, and antiviral effects. All day 0 and day 11 samples were tested for SI/NSI phenotype and for co-receptor use and viral tropism (CXCR4 or CCR5) using the PhenoSense assay. In this assay, virus stocks are produced by transfecting HEK 293 cells with a vector that expresses patient-derived HIV envelope sequences plus an HIV genomic vector containing a luciferase indicator gene. Co-receptor tropism is defined by assessing the ability of a virus to infect CD4. CCR5 cells and/or CD4. CXCR4 cells, and whether or not infection is inhibited by specific entry inhibitors. Viral tropism was independently confirmed by testing the ability of patient virus stocks derived from PBMC co-cultures to replicate in transfected cell lines.

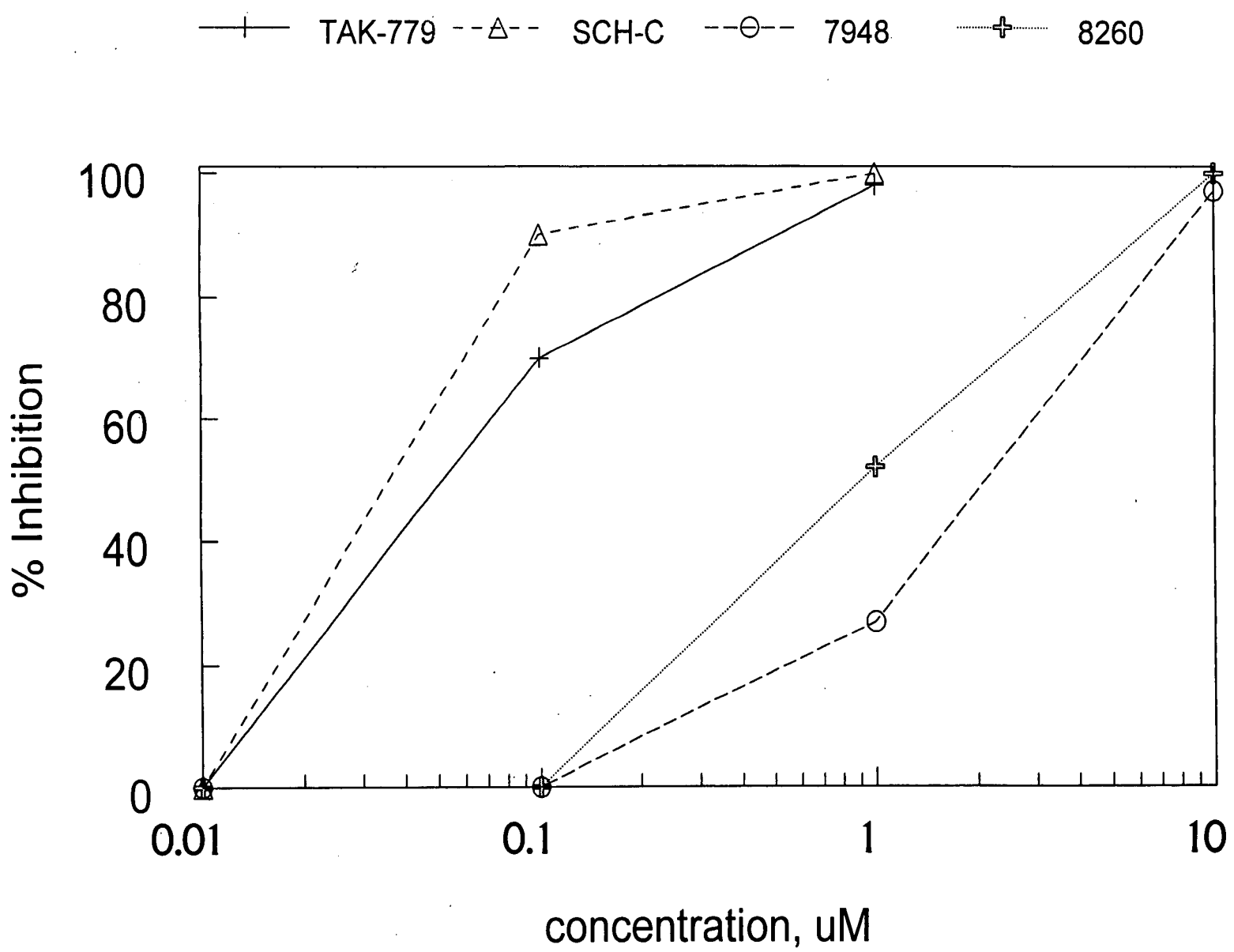
Results: 1 patient receiving AMD-3100 at 160 mcg/kg/h (a steady-state plasma concentration of 3.6 mcg/mL, no concomitant antiviral medications) exhibited a 0.8-0.9 $\log_{10}$ decrease in plasma HIV RNA by day 11 of treatment. Viruses from this patient on day 1 and day 11 were SI and exclusively used CXCR4, based on the PhenoSense assay and by replication of the virus stock in transfected cell lines. The virus stock was sensitive to AMD-3100 in PBMC, with an IC $_{50}$ (day 1 and day 11) of 16 and 18 ng/mL, respectively. Notably in 8 of 19 patients with dual (X4/R5) or mixed (X4+R5) virus at baseline, we observed a complete loss of X4 virus by day 11 of treatment. This was seen at 80 and 160 mcg/kg/h in 1 patient each and at 40 mcg/kg/h in 3/4. A loss of X4 virus was detected with a dose as low as 5 mcg/kg/h.

Conclusions: 1 patient with pure X4 virus, receiving AMD-3100, exhibited a viral load reduction that was virologically and phenotypically consistent with an antiviral effect. Also in 8 patients with dual or mixed virus at baseline, X4 viruses were no longer detected at day 11 at a dose as low as 5 mcg/kg/h. The PhenoSense assay accurately determined the co-receptor tropism of HIV from patient samples and may be used to predict drug susceptibility and virologic response.

Abstract 1 f 2: Topic PRO 140

The HIV-1 Entry Inhibitor PRO 140 Potently and Durably Suppresses Viral Replicati n *in vitro* and *in vivo*. W.C. OLSON[1], M. FRANTI[2], T.J. KETAS[1], K.A. NAGASHIMA[1], P.J. MADDON[1], D.R. BURTON[2], J. P. MOORE[3], and P. POIGNARD[2]. [1]Progenics Pharmaceuticals, Inc., Tarrytown, NY [2]The Scripps Research Institute, La Jolla, CA and [3]Weill Medical College of Cornell University, New York, NY.

Background: CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for antiviral therapy. PRO 140 is an anti-CCR5 monoclonal antibody that inhibits HIV-1 entry at concentrations that do not affect CCR5's chemokine receptor activity, and PRO 140 mediates genetic subtype-independent inhibition of HIV-1 replication in primary T cells and macrophages (Trkola *et al.*, J. Virol. 75:579, 2001). However, to date no published study has compared the potency and durability of viral suppression mediated by CCR5-targeting agents *in vitro* and *in vivo*. **Methods:** Viral sensitivity to PRO 140 following prolonged exposure to this agent was evaluated in PBMC culture *in vitro* and in a therapeutic animal model of HIV-1 infection (Poignard *et al.* Immunity 10:431, 1999). The *in vitro* studies employed the R5 biological clone HIV-$1_{CaseC\ 1/85}$ and a p24 readout, whereas the *in vivo* studies employed SCID mice reconstituted with normal human PBMC and later infected with the R5 isolate HIV-$1_{JR\text{-}CSF}$. Animals were treated with single and multiple intraperitoneal injections of PRO 140 and monitored for plasma viral RNA (Amplicor assay). **Results:** In both single-dose and multi-dose settings *in vivo*, PRO 140 potently and durably reduced viral loads to undetectable levels. In addition, viruses remained sensitive to PRO 140 following prolonged periods of exposure both *in vitro* and *in vivo*. **Conclusions:** PRO 140 demonstrated potent and sustained activity against primary viruses both *in vitro* and in a well-recognized animal model of HIV-1 infection. These findings underscore the therapeutic potential of CCR5-targeting agents in general and PRO 140 in particular.


TAK-779
SCH-C
7948
8260
100
80
60
40
20
0
% Inhibition
0.01
0.1
1
10
concentration, uM